EXPERIMENTAL STUDIES ON BLOOD ALCOHOL IN HEALTHY SUBJECTS AND IN SOME DISEASES

BY

S. G. JOKIPII

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HELSINKI 1951

EXPERIMENTAL STUDIES ON BLOOD ALCOHOL IN HEALTHY SUBJECTS AND IN SOME DISEASES

FROM THE FIRST MEDICAL CLINIC, UNIVERSITY OF HELSINKI
CHIEF: PROFESSOR WILLIAM KERPPOLA, M.D.

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BY

S. G. JOKIPII

ACADEMIC DISSERTATION

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PREFACE

On the suggestion of Professor William Kerppola, the chief of the First Medical Clinic, Helsinki, I started the present alcohological study in the spring of 1948, experimenting both on healthy subjects and on patients suffering from certain diseases. Professor Kerppola has with great interest observed the progress of my work from its beginning, has given valuable advice, and has encouraged me in my attempts to solve problems which often became rather complicated. In particular, he has helped and hastened the progress of my work by arranging laboratory facilities in his clinic and by advising me in the selection of the patients. I wish to express my great gratitude to him for all these matters which have in a decisive way contributed to the progress of my study.

I have had the privilege of relying upon the thorough knowledge of Dr. Antti Alha in problems connected with alcohol, and I am greatly indebted to him for this.

I have been much helped in the blood alcohol analyses by Miss Marja Muilu, laboratory nurse, and I wish to extend to her my best thanks for her help.

The mathematical treatment of the material was carried out by Mr Veikko Hauru, M. A., and I am very grateful to him for his contribution.

The translation into English was made by Mrs Annikki Toikka-Karvonen, M. A., and checked by Mr. F. W. Clement, both of whom I wish to thank for their kind co-operation.

I would further mention »Suomalainen Lääkäriseura Duodecim» (Finnish Medical Society Duodecim) and »Väkijuomakysymyksen Tutkimussäätiö» (Foundation for the Research of Alcohol Problems) from both of which I have received grants in support in my work.

Helsinki, February 1951.

S. G. Jokipii.

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I

REVIEW OF LITERATURE

The first investigations on the fate of alcohol in the organism were made just about hundred years ago. Some of the alcohologists of that period, for instance Bourchadat and Sandras (1847) came in their experiments to the conclusion that alcohol is almost completely oxidized in the organism. This view was supported by many authors in those days, but had also several opponents. The contrary opinion was expressed by Lallemand, Perrin and Duroy (1860), who claimed that alcohol, without being oxidized, is excreted from the body unchanged, mainly through the kidneys. Subbotin (1883) has made a quantitative study of the elimination of alcohol through the lungs, skin and kidneys of chicken, and has come to the conclusion that 16 per cent of the alcohol is excreted unchanged from the body. He remarked, moreover, that probably a considerable proportion of the alcohol excreted had not been recovered because of incomplete absorption in the alimentary tract. However, as early as 1875 Schmidt had arrived at the result that only 5 per cent of ingested alcohol is excreted from the organism unchanged, and of this amount only a quarter through the kidneys. According to Bodländer (1883) no significant amounts of alcohol remain unoxidized in the organism, and 95 per cent are metabolized to carbon dioxide and water. He further assumed that the absorption of alcohol from the alimentary tract was practically complete. According to the investigations of Atwater and Benedict (1902) 98 to 99 per cent of alcohol is oxidized in the organism.

Particularly valuable studies on the fate of alcohol in the organism were carried out by Gréhant (1896) just before the turn of the century. To him belongs the credit for having laid the foundation of modern research on alcohol, by studying the absorption of alcohol from the stomach, and by being the first to formulate the problems

of the blood alcohol curve. According to him, the blood alcohol level after the absorption of alcohol from the alimentary tract remains for some time at a stable level, the so-called Gréhant's plateau, a view which still is the subject of active research.

The great figure among the alcohologists around the turn of the century was Nicloux (1896). His most important achievement is the analysis of the distribution of alcohol in the body. In addition, he was able to recover almost entirely the ingested alcohol in blood and tissues. Similarly, he has demonstrated that the concentration of alcohol in blood depends on the amount of alcohol ingested. Pringsheim (1908) has treated of the elimination of alcohol from the organism. He has stated also that probably most of the oxidation of alcohol occurs in the liver. More or less similar findings have been presented by Batelli and Stern (1910) and Hirsch (1916). The investigations of Pringsheim (1908) as well as later studies by Schweisheimer (1913) have been important sources of reference for further alcohological studies, particularly in elucidating the individual tolerance to alcohol. Moreover, Schweisheimer was the first to determine the normal alcohol concentration of human blood. Investigations on the various aspects of the metabolism of alcohol have then appeared year by year. One of the most important among these is Mellanby's (1919) investigation on the absorption of alcohol from the alimentary canal and on its elimination from the blood. He made his experiments by administering alcohol to dogs by gavage. It is his opinion that the blood alcohol level rises the higher the more concentrated the solution of alcohol administered, when identical amounts of absolute alcohol are used. The same view has been expressed among others by Miles (1922) and by Tigerstedt and Kallioinen (1923), on account of experiments made on human subjects. Contrary results have been obtained by the Finnish alcohologist Tuovinen (1926, 1930). He has dealt with several problems of alcohology extensively and with merit in a dissertation published in 1930. He made his studies on five healthy subjects, by administering 60 ml of alcohol in 5, 20, 40, and 60 per cent solution to each of them and 40 ml in four experiments to one of them. He paid his main attention to two important problems, *i. e.* to the concentration of alcohol in the blood of the experimental subjects under standard conditions, and to the effect on the blood alcohol level of the concentration of the alcohol solution ingested.

He came to the conclusion that after ingestion of alcohol the blood level shows variations even in one subject under standardized conditions, and that dilute solutions of alcohol raise the concentration of alcohol in blood more than concentrated drinks do.

Carpenter (1929) again has studied the problems of the distribution of alcohol between the various tissues, by using chickens as experimental animals. Alcohol was administered to them in the form of an inhalation. He determined the concentration of alcohol in the various tissues of the body. His results demonstrate the important finding that after an ingestion of alcohol, the highest concentration of alcohol is met with in blood, and the lowest in adipose tissue and bone. Gréhant (1896) had already arrived at a similar conclusion.

Without doubt, the most important and most cited investigations on blood alcohol have been carried out by Widmark in the 'twenties. Widmark (1916) made his first studies by using the method of Nicloux (1896), and the later ones with his own modification (1918) of the former. Widmark (1916) arrived, for instance, at the conclusion that the strength of the alcohol ingested on an empty stomach has no notable effect on the blood alcohol level, and that the blood alcohol concentration produced by alcohol as ingested immediately after a meal is $^1/_5$ of that produced by an intake into an empty stomach. Widmark (1934) ascribed this finding, as also did Mellanby (1919), to the retarded absorption of alcohol and to a specific action of food on ethyl alcohol, for which reason the amount of alcohol absorbed from the intestine is reduced. According to him, proteins, and particularly amino acids, exert an important action of the latter type. Fat, carbohydrates, and water are without effect. Among others, Tuovinen (1930) has also stressed the rôle of proteins and, particularly, of a mixed diet. Southgate (1923), Kriebs (1934), Elbel (1937), Schmidt (1937), Neymark (1937) and Goldberg (1943) have similarly arrived at the result that an intake of food simultaneously with alcohol reduces the rise in the blood alcohol concentration, according to Schmidt (1937) by 16 to 20 per cent. The greatest achievement of Widmark (1932) in alcohology is the explanation of the rate of the oxidation of alcohol and of its diffusion in the organism. In the elimination phase, the alcohol level in blood shows a linear fall, according to him, and the rate of the oxidation of alcohol is independent of its concentration. In order to illustrate those processes, he has taken into use the

constants β and r. He has defined β as the decrease of the blood alcohol concentration per minute during the elimination phase of the blood alcohol curve, *i. e.* at a period when a diffusion equilibrium obtains between blood and tissues. In addition to this factor expressing the rate of the oxidation of alcohol, he has defined another constant, r, which gives a measure of the relation between the organism and the blood alcohol level. In defining the latter constant, Widmark has evidently had the advantage of Carpenter's (1929) studies. According to Widmark (1933), the constants β and r vary in different individuals, but he assumes that they are fairly constant in each subject.

It is perhaps due to Widmark's investigations that the years 1920 to 1930 became a period of active research in alcohology. In particular Kühn (1924) and Kionka (1928) have during that period made valuable studies, for instance of the normal blood alcohol level and of problems connected with it. The detailed investigations of Jungmichel (1933), Schmidt (1937), and Elbel (1937) particularly for the determination of Widmark's constants in German and Danish subjects deserve mention. Haggard and Greenberg (1934) have made experiments by injecting alcohol intravenously to experimental animals, and drawn the conclusion that the metabolism of alcohol is an exponential reaction, and that the rate of the oxidation of alcohol is directly proportional to the concentration of alcohol. This view has also been represented by Newman, Lehman and Cutting (1937) and by Eggleton (1940). However, Neymark (1936) in collaboration with Widmark has confirmed the validity of Widmark's theory, *i. e.* that the rate of the oxidation is independent of the concentration of alcohol. Similar results have been published by Jungmichel (1933), Schmidt (1937), Elbel (1937) and by Goldberg (1943). The resorption and oxidation of alcohol has been studied particularly in alcoholics by Bernhard and Goldberg (1935), who came to the conclusion that the constants β and r are about equal in alcoholics and abstainers. The blood alcohol curve of the alcoholics differs from that of abstainers only in the respect that the resorption maximum is reached in alcoholics slightly earlier than in abstainers, and that the blood alcohol level in the former rises a little higher than in the latter. In a later study, Goldberg (1943) has observed that in alcoholics the rate of the oxidation is somewhat faster than in abstainers. Broggi (1933) claims on the contrary to have observed

a slower rate of oxidation in alcoholics, but his conclusion is probably erroneous, because he has compared the values which were obtained from alcoholics — and which were within the limits of published normal values presented in literature — with the respective figures of his own control material (3 subjects).

The number of alcohological studies made on clinical patients is less. Dell'Acqua (1932) has studied the blood alcohol curves of some cases of diabetes and hyperthyreosis and compared them with normal values. It is commonly accepted that the oxidation of alcohol occurs mainly in the liver. Serianni and Lolli (1938) have been the first to suggest an alcohol tolerance test as a test of liver function. Erwteman and Heeres (1938), while making clinical and experimental observations on the alcohol tolerance in some liver diseases, diabetes, hyperthyreosis, and heart and lung diseases, have discovered a typical and specific blood alcohol curve in acute hepatitis, liver cirrhosis and liver tumours, and because of this they claim that the alcohol tolerance test is useful in the differential diagnosis of liver diseases. Further, Staub and Peyser (1945) have stated: »Eine wesentliche Rolle für die Alkoholoxydation können auf jeden Fall extrahepatische Orte nicht spielen» and made the conclusion that the rate of the oxidation of alcohol might be used in testing the hepatic function. They also stated that the blood alcohol curves of hepatocellular and obstruction icterus differ from each other, and suggest the use of an alcohol tolerance test in the differential diagnosis. Josephson and Asplund (1948) made six experimental subjects drink 30 ml of 40 vol. per cent alcohol, and studied the effects on liver by using a battery of tests and reactions. Positive results remained fairly meagre; in four subjects a slight reduction in prothrombin was observed, but according to their opinion, there are also persons sensitive towards alcohol. According to Josephson and Asplund (1948), liver cirrhosis which occasionally occurs in alcoholics is not caused primarily by the toxic action of alcohol on liver, but rather by the poor and unbalanced quality of the nutrition, digestive disturbances, avitaminoses, etc. A summarizing presentation by Jellinek (1942) of the causal relationship of alcohol and liver cirrhosis is very comprehensive and perspicuous. Möllerström (1945, 1947) has in several papers dealt with the subject of endogenous alcohol, particularly in diabetes and in chronic alcoholics.

Among recent work on alcohol, several papers by Newman (1935,

1936, 1937, 1949) deserve mention, some of them made in collaboration with Lehman, Cutting and Yee. The experiments have been made by administering alcohol intravenously, mainly to dogs and rats, and they deal with alcohol tolerance and the previously mentioned relation between the rate of oxidation and the concentration of alcohol. Cutting, Newman and Yee (1949) make the following conclusion from their results: »The rate at which ethanol is metabolized in the dog bears a relationship to the concentration of the alcohol in the animal body, the higher the concentration the higher the rate.»

Gremels (1948) has stated that when alcohol and sucrose or laevulose are administered simultaneously, both the alcohol and the sugar concentration in blood rise very little. Thus, the central effect of even great amounts of alcohol remains small. According to him, alcohol is oxidized more rapidly in the presence of sugar. Bartlett and Barner (1949) have carried out studies on the metabolism of alcohol by using radio-active ethanol labelled with C_{14}. They observed that 75 per cent of the alcohol is oxidized to carbon dioxide within 5 hours, 90 per cent in 10 hrs., and that this process occurs, according to studies with tissue slices, most rapidly in liver and kidneys, but slowly in heart and diaphragm. They found that brain tissue had no effect on the oxidation of alcohol. They lay stress on the finding that the rate of the oxidation is the same in normal animals and in animals accustomed to alcohol.

The literature on blood alcohol is very extensive, and its exhaustive treatment in this connection serves no purpose. Therefore, the writer's aim has been only to give an outline of problems associated with the metabolism of alcohol.

II

METHODS

A number of physico-chemical and chemical methods have been developed for the determination of alcohol in blood. As early as in 1875, Heubach, and a little later, Bodländer (1883) have described a method for the determination of the concentration of alcohol in blood by using the Geissler vaporimeter. However, this method has not proved so suitable in the determination of small amounts of alcohol. Therefore, Bodländer (1883) himself used the dichromate method in analyses containing less than 0,5 ‰ of alcohol. The method of Kionka from 1924, later modified by Hirsch and Bock, is well known and rather commonly used. It is based on the interferometric determination of alcohol in the distillate. However, in serial determinations the method has not gained acceptance, partly because it requires a great amount of blood, partly because it is not specific to alcohol. Still, this method is used to a considerable extent in forensic medicine.

Newman and Abramson (1942) have described a method for the colorimetric determination of ethyl alcohol, by using a photoelectric colorimeter. The alcohol is distilled from saturated sodium sulphate at 50 to 55°C to a solution of potassium dichromate in concentrated sulphuric acid, and the concentration of dichromate is determined with a photoelectric colorimeter. Henry, R., Kirkwood, Berkman, Housewright and Henry, J. (1948) have developed a method which is based on the oxidation of alcohol to acetaldehyd, and this is determined colorimetrically, by using p-hydroxydiphenyl as a reagent. They regarded this method as particularly sensitive.

A considerable portion of blood alcohol determinations have been carried out by chemical methods based on the reduction of dichromate. To these belongs for instance the method of Cotte (1852), where alcohol reduces the dichromate, and the surplus of

dichromate is titrated with ferrous ammonium sulphate, using potassium ferricyanide as an indicator. This method has been used for instance by Pringsheim (1908) and Mellanby (1919). Well known is the method of Nicloux from 1896, which is also based on the oxidation of alcohol. In this method potassium dichromate is reduced to chromic sulphate, using concentrated sulphuric acid as an absorbent. Such a solution is bluish green, and when more potassium dichromate is added, the colour changes to yellow green. However, the reaction is not very reliable, and there are great sources of error, not least due to judging the colour. Nicloux has later on (1931, 1934) modified this so-called macromethod of his to a micromethod, and it is still fairly often used and esteemed. The disadvantage of it is that a relatively great volume of blood is needed for an analysis. Therefore, several investigators have pointed out that the method is cumbersome, particularly, if many samples are to be drawn from the subjects during an experiment (Schmidt 1937, Hoffmann 1937, Elbel 1937). Several modifications of this method exist, as those of Atwater and Benedict (1898), of Schweisheimer (1913), of Widmark (1918) and of Hansen (1924). The latter method has been used for instance by Tuovinen (1926, 1929, 1930) in his studies.

Probably the most commonly used quantitative micromethod for the determination of alcohol in blood is that published by Widmark (1922) and later (1932, 1934) modified by him. It is based on the oxidation of alcohol to acetic acid by means of dichromate-sulphuric acid, and on the iodometric determination of the surplus of dichromate. Widmark's micromethod has been employed for instance in the studies of Olow (1923), Schwartz (1927), Lundsgaard (1932), Jungmichel (1933), Kriebs (1934), Bernhard and Goldberg (1935), Schmidt (1937), Hoffmann (1937), Elbel (1937), Tuovinen (1937), Goldberg (1943), Österlind, Åhlen and Wolff (1944), Möllerström (1947), of the investigators committed by the Finnish Blood Alcohol Committee (1949), and of Hald, Jacobsen and Larsen (1949).

The iodide method of Fraenckel-Nicolai (1928) is evidently rather specific to alcohol, but it is all too cumbersome in clinical use. In the method, ethyl alcohol is heated with a surplus of hydriodic acid, which produces ethyl iodide. This is changed with the aid of silver nitrate to silver iodide, the amount of which is determined gravimetrically. Newman (1936) has developed an iodometric

method, and the method of Eggleton (1940) is some kind of modification of this.

Friedemann and Klaas (1936) have published a method which is based on the oxidation of alcohol in alkaline permanganate solution. Mercuric tungstate is used in the method in order to prevent the effects of aldehydes and ketones, and calcium hydroxide to bind oxidating substances. Möllerström (1945) has used this method in parallel with Widmark's method, when investigating the blood alcohol of diabetic patients. However, it is complicated and technically rather difficult.

Cavett (1938) has presented a titration method, which resembles Widmark's micromethod. Gettler and Umberger (1942) have published a method where an alcaline medium is used, claimed to be specific for alcohol, and suitable for amounts greater than 0.02 mg of alcohol. When estimating the amount of alcohol in blood, however, this method requires the use of 5 ml samples of blood, and in serial determinations on the same subject this method is not practical.

McNally and Coleman (1944) have described an apparatus for the titration method. However, the system seems fairly complicated, in order to be employed in clinical series of analyses.

III

PURPOSE OF THE PRESENT WORK

In spite of the great amount of published work on blood alcohol, the Finnish material remains, however, limited in certain respects. In addition to the aforementioned studies by Tuovinen (1926, 1930) on the concentration of alcohol in blood under varying conditions and after the ingestion of alcohol of varying strengths, the Blood Alcohol Committee appointed by the Government (1949) has performed the determination of Widmark's constants β and r for the Finnish population. Twenty males were used as experimental subjects, ten of them being intellectual workers and ten car drivers by trade.

Because the blood alcohol determinations have mainly been carried out on male subjects, and moreover, because the above results for the Finnish population were derived from experiments made exclusively on men, the writer regarded it as desirable to determine Widmark's constants β and r also on a group of healthy Finnish women, and to compare the values thus derived with values obtained on healthy men. It is of practical importance to be able theoretically to calculate the blood alcohol concentration at a time for instance when there was no opportunity to take a blood sample, as well as to control the amount of alcohol reported having been consumed at a certain time, both presuming a knowledge of the maximum, minimum and average values of the constants β and r in the population.

Since a great proportion of patients suffering from neurocirculatory asthenia or dystonia, or of diabetes mellitus, are comparable with normal persons, so far as their social activities and everyday life are concerned, and since the case history of a patient belonging to the type of neurocirculatory asthenia generally reveals a poor alcohol tolerance, the writer studied whether any differences

are to be observed in the alcohol metabolism between patients belonging to the above groups and healthy subjects, particularly in the rate of the elimination of alcohol and in its diffusion in the body; moreover, a study was made of the so-called basal values (the normal alcohol and other easily oxidized volatile substances) in the blood of abstaining healthy subjects and of diabetic patients, by using Widmark's micromethod. The following terms have also been used for this concept: normal, endogenous, physiological alcohol etc.

Further, the writer investigated whether some liver diseases (acute hepatitis, liver cirrhosis) and hyperthyreosis have any effect on the level of blood alcohol after the ingestion of alcohol (0.5 g/kg). The problems, in short, were as follows:

1. *What are the characteristics of the alcohol metabolism of the Finnish woman?*
2. *Does the alcohol metabolism show any deviations from normal in some internal diseases (neurocirculatory asthenia or dystonia, acute hepatitis, liver cirrhosis, hyperthyreosis, diabetes mellitus)?*
3. *What is the concentration of endogenous alcohol in the blood of fasting healthy subjects and of diabetic patients, respectively?*

IV

SELECTION OF METHOD AND TECHNIQUE

The author made the blood alcohol determinations by using Widmark's micromethod. This method is the one most employed, at least in blood alcohol studies mentioned in the European literature. It is relatively simple, fairly easy to learn and master. The reliability of the method and the sources of error to be considered have been analysed by several workers (Linde 1932, Jungmichel 1933, Kriebs 1934, Elbel 1937, Hoffmann 1937, Schmidt 1937, Kanitz 1939, Graf 1949). Many investigators have given a favourable criticism of the applicability of the method to the determination of alcohol in blood. The coefficient of dispersion of this method has been assessed by Jungmichel (1933) at 0.028 $^0/_{00}$, by Schmidt (1937) at 0.034 $^0/_{00}$, and by Bjerver, Goldberg, Herzenberg, Lundberg and Ottoson (1949) at 0.03 $^0/_{00}$.

The great advantage of Widmark's micromethod in serial studies is the small amount of blood needed. Moreover, the distillation, absorption and the oxidation of the alcohol occur in one and the same closely stoppered Erlenmeyer flask, and thus the loss of alcohol can be entirely avoided.

It is true that the method is not specific to alcohol, but it shows the concentration of all easily oxidized volatile substances in blood. This is true also of almost all the other methods. There are normally in the blood such substances, as lactic acid, glycerol, acetaldehyde, ammonia, fatty acids etc., but only in minute amounts, and they have no practical significance in assessing values obtained by means of Widmark's method. Much more attention must be paid to the occurrence in blood of acetone, acetoacetic acid, and of β-oxybutyric acid. It is true that they are not met with expect in pathologic conditions, as in connection with a long period of fasting, and the fasting overnight and for six hours during the experiment can not

be regarded as such. For all we know the concentration of ketone bodies in the blood of normal subjects never exceeds 0.02 $^0/_{00}$ (Widmark 1917). According to Kirk (1942) their concentration in plasma may normally rise to 0.01—0.02$^0/_{00}$. However, in diabetic patients rather high concentrations of ketone bodies in blood may be observed. Still, this generally occurs only during a severe comatose state (Widmark 1917, Kohberg 1930, Schmidt 1937). In spite of the fact that the concentration of ketone bodies in the blood of an ordinary diabetic patient not in praecoma or coma is evidently relatively small, a qualitative test of the urinary acetone and acetoacetic acid ought always to be made, by means of Gerhard's and Legal's tests, which practice has been followed by the present writer. Because the kidneys show a low threshold value for the excretion of these compounds, a small rise of ketone bodies in blood can not be discovered with these tests.

It is obvious that foreign alcohol or aether may not be present, when the analysis is made. Therefore, the skin is cleaned with mercuric chloride. Other possible errors in the performance of the method have been so accurately described in the literature that there is no reason to dwell on them in this connection (Jungmichel 1933, Elbel 1937, Schmidt 1937, Kanitz 1939, etc.). Meticulous accuracy, thorough training and due consideration to the sources of error as mentioned in the literature make the method a reliable one.

The following solutions are needed for the analysis:

1. Dichromate-sulphuric acid solution.
2. 5 per cent iodate-free potassium iodide solution.
3. *n*/100 sodium thiosulphate solution.
4. 1 per cent starch solution as an indicator.

After the tip of the finger has been cleaned with the mercuric chloride solution (1:1000) and dried with cotton wool, a small wound is made with Francke's needle, and blood is made to flow into two or three of Widmark's S-shaped capillaries. The capillaries are closed with stoppers, and the blood samples thus taken may be kept in a refrigerator for being analysed as late as after a few days. However, the writer has made all the analyses without exception during the same afternoon.

After that, the potassium dichromate-sulphuric acid solution is transferred to Widmark's flasks, by using Hohn's syringe as described by Kriebs (1934). The flasks must be meticulously cleaned before each experiment. Attention must be paid to transferring exactly identical volumes of the dichromate solution to each flask, these amounts being in surplus to the amount of alcohol. Therefore, exactly 1 ml was taken for instance in the analyses described in the present work.

The flasks containing both the analysis and the blanks are then put in special stands into an easily regulated electrically heated water bath where the temperature is kept at 55°C. After 5 min. they are taken from the water bath, and the blood contained in the capillaries, after having first been weighed in Bang's torsion balance, is carefully blown by means of a rubber tube into a special cup hanging above the surface of the dichromate solution and being attached to a close stopper of the flask. After this, the flasks are again left in the water bath for two hours.

After the incubation, the small cups are carefully removed without spilling any dried blood into the flask. Then, 25 ml of distilled water is poured along the wall into each flask, and 0.5 ml of the potassium iodide solution is added. Titration with the thiosulphate solution can now be started, stirring the contents of the flask cautiously all the time. When the yellow-brown colour begins to go lighter, a few drops of the starch solution are added, and the titration is carried on until the colour entirely disappears.

As 0.5 g of potassium dichromate in 200 ml of concentrated sulphuric acid and $n/100$ sodium thiosulphate were the solutions used, a factor 1.13 has been used as Widmark's constant in the calculations (Widmark 1922). The validity of this factor has been confirmed later on by several authors (Jungmichel 1933, Schmidt 1937, etc.). 1.13 γ (γ = 0,001 mg) of alcohol corresponds to 0.01 cc of $n/100$ sodium thiosulphate solution; the difference between the amount of thiosulphate in ml used in the titration of the blank and of the analysis when multiplied with 1.13 indicates the amount of alcohol in γ. This figure must be divided with the weight of the blood contained in the capillary in order to get the concentration of alcohol in $^0/_{00}$ in the sample analysed.

The formula of the calculation:

$$\frac{(a - o) \times 113}{p} = \text{concentration of alcohol in } {}^0/_{00};$$

a = ml of thiosulphate used in analysis;
o = ml of thiosulphate used in blank;
p = weight of the blood in the capillary in mg.

V

GROUPING OF THE MATERIAL

The present study was started in the spring of 1948, and the collecting of material was carried on until April 1950. The material used for the determination of the blood alcohol after an administration of alcohol was collected so that the groups of patients suffering from certain diseases (neurocirculatory asthenia or dystonia (NCA), acute hepatitis, liver cirrhosis, hyperthyreosis, and diabetes mellitus) were under treatment at the First Medical Clinic of the University of Helsinki, except for a few cases of NCA and hyperthyreosis treated as outpatients. The diagnoses of these patients also were duly confirmed before their inclusion in the material. The patients of this hospital come almost exclusively from the rural areas, mostly from the surroundings of Helsinki, and are mainly manual workers.

In collecting a control material from outside the hospital an attempt was made to include only those really healthy, so far as could be judged from the history and from a thorough general examination. The latter group comprises both manual and intellectual workers: firemen, drivers, technicians, nurses, and office workers. These people generally belonged to a somewhat younger age group than the patients, which was due to the fact that, in spite of attempts, it turned out impossible to persuade older healthy people to volunteer as experimental subjects.

The basal value was determined on the above control group and, moreover, on a group of healthy nurses and student nurses.

The material comprises altogether 135 experimental subjects; each of them serving for duplicate or triplicate blood alcohol determinations with Widmark's method at suitable intervals. Determinations of the endogenous blood alcohol were made on 165 blood samples taken from 74 subjects. Blood alcohol determin-

ations after an ingestion of alcohol were performed on 1420 samples of blood taken from 124 subjects. The material is divided as follows:

A. The determination of the endogenous blood alcohol.

a. Healthy subjects.
This group comprised 53 subjects, of these 19 male and 34 female.

b. Diabetic patients.
Their number was 21, of these 13 male and 8 female.

B. The determination of blood alcohol after an administration of alcohol to healthy subjects.

The number of the subjects was 42, of these 19 male and 23 female. Three cases of obesity, and one female patient of exceptional thinness are also presented separately in connection with this group, for the purpose of comparison.

C. The determination of blood alcohol after an administration of alcohol to patients suffering from some internal diseases. This group comprises altogether 78 patients, distributed as follows:

a. Neurocirculatory asthenia.
The number of cases was 17, of these 11 male and 6 female.

b. Acute hepatitis.
The number of cases was 19, of these 8 male and 11 female.

c. Liver cirrhosis.
This group comprised 5 patients, 4 male and 1 female. A case of carcinoma of liver is also presented with this group.

d. Hyperthyreosis.
The number of cases was 15, of these 3 male and 12 female.

e. Diabetes mellitus.
21 experimental subjects, of these 13 male and 8 female.

In determining the basal values, a blood sample was taken from the experimental subjects into 2 or 3 Widmark's capillaries, from some subjects at 4 or 5 different times. The subjects, except the diabetic patients who were treated in the hospital, arrived early in the morning for the taking of the blood samples. They had been without food and drink as from the previous night, *i.e.* approximately 10 to 12 hrs., and the abstinence was continued during the experiment,

when several samples were taken. The subjects had to abstain from alcohol for at least two days before the experiment. This was, of course, easy to control in the hospital patients, but in the case of subjects coming from outside the hospital, one had to rely upon their word. The diabetic patients of the material were left without insulin on the morning of the experiment, and, of course, during the experiment itself. If such a patient was being treated with retarded insulin, the administration was omitted also on the morning of the preceding day. When investigating the basal values of the diabetic patients, the blood sugar concentration was also determined, by using the method of Hagedorn-Jensen, and the urine was tested for sugar and ketone bodies with Nylander's, Gerhard's and Legal's tests.

Those experimental subjects, the healthy ones as well as the patients, who were given alcohol for the determination of blood alcohol, were first weighed in order to know the amount of alcohol to be administered. All the experimental subjects received 0.5 g of absolute alcohol as calculated per kg body weight, given as 40 per cent (by weight) aqueous solution on an empty stomach. For the sake of uniformity, greater doses of alcohol were not given, because the material also contained patients suffering from jaundice, to whom a greater dose was not regarded as desirable. The withdrawal of food and drink was the same in this group as in the basal group. The abstinence could be confirmed by taking a sample of blood for determination of alcohol before starting the actual experiment. This factor was under control in the hospital patients. The assurance of abstinence by the other subjects also appeared reliable, as this so-called fasting value in most cases of the material was 0.000 $^0/_{00}$, and even in those cases in which this was exceeded, it remained within those limits regarded in literature as being normal (Kühn 1924, Handwerk 1927, Schmidt 1937, etc.).

The performance of the experiments was regularly started early in the morning, when the hospital patients came for the experiment straight from their beds, the others walking or arriving by some means of conveyance. After a sample for the so-called fasting value was taken, the subject was made to drink his dose of alcohol as fast as possible. In general, this took about 3 minutes. After this, the subject was allowed to rinse her or his mouth with water, without swallowing it, in order to get rid of the taste of alcohol, and thus to

reduce an eventual nausea. All subjects expect two stood the alcohol well. These two, also, were able to take the alcohol well when the experiment was later repeated. The subjects were during the whole experiment at complete rest, lying on a bed.

Thus, it was easy to observe the continuous keeping of the absolute fast, as well as the reaction of the subjects to alcohol, nausea, sickness etc. It was also possible in this way to exclude the eventual effects of muscular work on the shape of the blood alcohol, curve. It is a common opinion that muscular work does not increase the rate of the oxidation of alcohol (Widmark 1930, 1941, Meyer 1931, Dell'Acqua 1932, Nyman and Palmlöv 1934, Schmidt 1937, etc.). However, contrary opinions have also been expressed (Rosemann 1925, etc.).

The samples for the blood alcohol determination were taken at 20, 40, 60, 90, 120, 150, 200, 250, 300, and 350 minutes after the ingestion of the alcohol.

The diabetic subjects were without insulin in the same way as at the determination of the basal values of this group. Similarly, a determination of the blood sugar, and a qualitative test for urinary sugar and ketone bodies were made in the diabetes cases in parallel with Widmark's blood alcohol determination. These determinations were made at 60, 120, and 300 minutes after the ingestion of alcohol.

On the hepatitis patients, the icterus index of serum was determined and a qualitative test for urinary bilirubin, urobilinogen and urobilin was made by using Rosin-Trousseau's, Ehrlich's and Schlesinger's reactions. In most cases of jaundice and in all cases of liver cirrhosis, some other tests of the hepatic function were also performed, such as the Takata, thymol and phosphatase tests.

Futhermore, 11 of the patients suffering from acute hepatitis were subjected to a control study, and 3 to two controls, either during recovery from the illness or after it, in order to discover, whether the alcohol tolerance curve changes when the icterus index falls and the patient recovers.

Similarly, it was originally the purpose to make a control study of hyperthyreotic patients after the medical or surgical cure of the disease. However, it proved impossible to get more than three patients given a medical treatment and one patient given a surgical treatment to a follow-up examination. No certain conclusions can, of course, be made from such a small material.

VI

ENDOGENOUS ALCOHOL IN THE BLOOD OF HEALTHY SUBJECTS

PREVIOUS STUDIES

The normal alcohol content of the blood of animals has been known considerably earlier than that of human blood (Ford 1859, Rajewsky 1874, Pringsheim 1908). According to Ford's (1859) views, the endogenous alcohol is a product of the decomposition of the carbohydrates of the diet.

As already mentioned, Schweisheimer (1913) was the first quantitatively to determine the normal alcohol concentration of human blood. He used the method of Nicloux, and found that the alcohol concentration in the blood of fasting man was on an average 0.029 $^0/_{00}$, with a range from 0.019 to 0.046 $^0/_{00}$. According to his investigations, food had no great effect on the concentration of alcohol. Thus, after the intake of food he found an average concentration of 0.036 $^0/_{00}$. Similar studies were later carried out by Miles (1922), who obtained values approximately identical with those of Schweisheimer (1913). A little later, Kühn (1924) determined the endogenous alcohol content in the blood of 17 fasting students, by using the interferometric method of Kionka-Hirsch. The average value obtained by him was 0.021 $^0/_{00}$, and the range extended from 0.006 to 0.051 $^0/_{00}$. However, he regarded the values of 14 subjects only as correct, and then the corresponding figures were: average 0.015 and range from 0.006 to 0.021 $^0/_{00}$. According to Kühn's (1924) observations, the normal alcohol concentration of blood varies, not only in different subjects, but also in one and the same subject. Handwerk (1927) has obtained the figure of 0.010 for the concentration of the normal blood alcohol. Kionka (1928), similarly

using the method of Kionka-Hirsch, has obtained a range from 0.01 to 0.06 ‰ and an average of 0.031 ‰ for the normal blood alcohol of fasting subjects; in non-fasting subjects the range was from 0.015 to 0.21, and the average 0.052 ‰.

Aoki (1925) has made extensive investigations on the formation of the endogenous alcohol, confirming the view of some of the earlier investigators that the normal blood alcohol is a product of the normal carbohydrate metabolism. This view has been supported by several alcohologists, for instance by Heilner (1924), Kionka (1928), and by Schmidt (1937).

Tuovinen (1930) has found from 0.03 to 0.05 ‰ of normal alcohol in the blood. He has in his investigations adopted the view that the endogenous alcohol is a product of the microbial degradation of carbohydrates in intestine.

Further, the normal blood alcohol content has been studied by Matossi (1931), Dell'Acqua (1932), Gettler, Niederl and Benedetti-Pichler (1932), Jungmichel (1933), Kriebs (1934), Friedemann and Klaas (1936), Schmidt (1937), Henry *et al.* (1948) and Bjerver *et al.* (1949). The values obtained by Matossi (1931) vary between 0.02 and 0.14 ‰, and those of Dell'Acqua (1932) between 0.002 and 0.12 ‰. Gettler *et al.* (1932), Jungmichel (1933) and Kriebs (1934) estimated the concentration of the endogenous alcohol at 0.03 ‰. Schmidt (1937) has observed an average concentration of normal blood alcohol of only 0.017 ‰ in fasting subjects, Bjerver *et al.* (1949) 0.01 ‰. Among the 41 subjects studied by Schmidt (1937), in 12 the concentration of the normal blood alcohol was 0.000, in 10 0.01, in 8 0.02, in 6 0.03, in 3 0.04, in one 0.06, and in one 0.09 ‰. The two latter investigations were both made by using Widmark's micromethod. Henry *et al.* (1948) have determined the endogenous blood alcohol in 30 healthy subjects, obtaining also lower values than those generally mentioned in the literature, *i. e.* 0.006 ‰, with a range from 0.001 to 0.010 ‰.

The investigations on the normal blood alcohol have been performed by using various methods and the values obtained differ from each other (Table 1). However, the concentrations are so small that they do not exceed the methodical error and thus do not really affect the results of the alcohol analyses proper. Moreover the values obtained in the latest investigations on the endogenous alcohol are considerably smaller than those previously observed,

TABLE I

ENDOGENOUS ALCOHOL (BASAL VALUES), IN THE BLOOD ACCORDING TO SOME INVESTIGATORS

Year	Investigator	Method	Concentration of alcohol o/oo	Maximum	Minimum	Notes
1913	Schweisheimer	Nicloux	0.029	0.046	0.019	Fasting
1922	Widmark	Widmark	0.03	0.054	0.019	No fast
1924	Kühn	Kionka-Hirsch	0.021	0.051	0.006	Fasting
1926	Baglioni, Bracaloni and Salamini	Widmark modified	0.024—0.06	0.07	0.011	Fasting
1927	Kionka	Kionka-Hirsch	0.031	0.06	0.01	Fasting
1927	Handwerk	Kionka-Hirsch	0.0107	0.037	0.000	
1927	Gettler and Tiber	Gettler	0.015			Fasting
1930	Tuovinen	Hansen	0.03—0.05			Fasting
1931	Matossi	Nicloux		0.14	0.02	
1932	Gettler, Niederl and Benedetti-Pichler		0.04			
1932	Dell'Acqua	Widmark	0.038	0.12	0.002	Fasting
1933	Jungmichel	Widmark	0.03			
1934	Kriebs	Widmark	0.03	0.068	0.000	No fast
1936	Friedemann and Klaas	Friedemann - Klaas		0.004	0.001	
1937	Schmidt	Widmark	0.017	0.09	0.000	Fasting (4-6 hrs.)
1948	Henry et al.	Henry et al.	0.006	0.010	0.001	Fasting
1949	Bjerver et al.	Widmark	0.01			Fasting
1951	Own investigations	Widmark	0.012	0.068	0.000	

which may to a great extent be due to a more strict elimination of methodical errors in the recent work.

OWN INVESTIGATIONS

The endogenous blood alcohol was determined on 19 healthy male and 34 healthy female subjects, after an abstinence from alcohol for two days and a fast of 12 hours. In each case, the determinations were made either in duplicate or in triplicate. In addition, the value was determined in 13 female subjects at 4 different times during a 5 hours' period. The determinations in this group were made on 91 blood samples in whole.

For the men, an average value of 0.007 ‰ was obtained, with a range from 0.000 to 0.030 ‰ (Table 2).

TABLE 2

ENDOGENOUS ALCOHOL (BASAL VALUES) IN THE BLOOD OF HEALTHY MEN AS DETERMINED WITH WIDMARK'S MICROMETHOD

Subject	At 7.00 a.m.
O.H.	0.000
M.P.	0.019
P.O.	0.000
K.K.	0.016
R.I.	0.030
I.N.	0.000
J. J.	0.000
R.N.	0.030
P.S.	0.014
S.J.	0.006
P.E.	0.000
B.B.	0.000
V.I.	0.019
O.S.	0.000
T.J.	0.000
A.P.	0.000
M.L.	0.000
A.A.	0.000
T.V.	0.000 ‰

For the endogenous alcohol of *the women of* 0.014 ‰ was found, with a range from 0.000 to 0.066 ‰ (Table 3).

TABLE 3

ENDOGENOUS ALCOHOL (BASAL VALUES) IN THE BLOOD OF HEALTHY WOMEN, AS DETERMINED WITH WIDMARK'S MICROMETHOD

Subject	7.00 a. m.	9.00 a. m.	11.00 a. m.	12.00 a. m.	Mean
K. J.	0.039	0.045	0.067	0.029	0.045
R. V.	0.000	0.008	0.000	0.000	0.002
S. H.	0.013	0.000	0.000	0.000	0.003
T. K.	0.008	0.000	0.000	0.000	0.002
K. M.	0.000	0.015	0.000	0.000	0.004
K. V.	0.008	0.005	0.006		0.006
S. M.	0.036	0.036	0.028	0.030	0.032
O. V.	0.030	0.067	0.046	0.064	0.051
H. V.	0.000	0.019	0.000	0.004	0.005
M. V.	0.005	0.005	0.008	0.000	0.004
E. H.	0.009	0.029	0.028	0.022	0.022
I. M.	0.008	0.000	0.003	0.005	0.005
S. H.	0.007	0.004 ‰	0.018 ‰	0.010 ‰	0.009 ‰
T. H.	0.000				
S. P.	0.030				
M. L.	0.000				
S. Hi.	0.034				
M. S.	0.020				
E. K.	0.000				
S. K.	0.045				
S. Ka.	0.028				
P. H.	0.005				
E. N.	0.020				
M. O.	0.015				
S. J.	0.066				
E. R.	0.000				
I. M.	0.003				
Sy. J.	0.006				
K. M.	0.000				
A. V.	0.000				
S. V.	0.000				
M. Vu.	0.000				
E. T.	0.006				
E. A.	0.012 ‰				

In the majority of the men, the concentration of the endogenous alcohol was 0.000 ‰. In women, most values lied between 0.000 and 0.005 ‰ (Table 4).

In *the material as a whole*, the average endogenous alcohol concentration was 0.012 ‰.

TABLE 4

ENDOGENOUS ALCOHOL (BASAL VALUES) IN THE BLOOD OF HEALTHY SUBJECTS, ARRANGED IN GROUPS ACCORDING TO THE NUMERICAL VALUE

Basal alcohol ‰	Males	Females	Total
0.000	12	8	20
0.001—0.005	0	9	9
0.006—0.010	1	4	5
0.011—0.015	1	2	3
0.016—0.020	3	2	5
0.021—0.025	0	1	1
0.026—0.030	2	2	4
0.031—0.035	0	2	2
0.036—0.040	0	0	0
0.041—0.045	0	2	2
0.046—0.050	0	0	0
0.051—0.055	0	1	1
0.056—0.060	0	0	0
0.061—0.065	0	0	0
0.066—0.070	0	1	1
Total	19	34	53

VII

ENDOGENOUS ALCOHOL IN THE BLOOD OF DIABETIC PATIENTS

PREVIOUS STUDIES

A considerable increase during recent years in the use of alcohol in connection with the driving of motor vehicles has given a stimulus to the investigation of the normal alcohol content of the blood of diabetic patients. As diabetic patients may, as well as healthy people, cause motor accidents, it has been observed that the commonly used micromethod of Widmark may at a police examination in some cases of diabetes give high enough values even to exceed the statutory limits of blood alcohol. This limit varies in different countries between 0.5 and 1.5 $^0/_{00}$. There lies, therefore, the danger that a diabetic patient who has not ingested any alcohol may, in the case of an accident, be punished if a high value is obtained with Widmark's method at a blood alcohol determination following the accident. It must be noted that Widmark's method, as the oxidation methods in general, is not specific to alcohol, but indicates the oxidizable, volatile substances in the analysis. The interferometric methods are probably still more unspecific. The Swede Möllerström (1945, 1947) who has during recent years investigated the amount of the endogenous alcohol in the blood of diabetic patients, using a very large material, has used the methods of Widmark and Friedemann-Klaas in parallel. According to him, the latter method should indicate the real alcohol concentration in the analysis. On the strength of his studies, he reports that the values obtained with Widmark's method have in general been 0.000 $^0/_{00}$ or only quite insignificantly higher. His view is that not all diabetic patients are alcohol-formers, but that there are chances of the formation of alcohol in such persons. He states as an argument

for this that there occur in the normal intermediary metabolism of carbohydrates processes similar to those in the usual fermentation of alcohol. Möllerström (1947) has observed that the basal alcohol concentration of the blood of diabetic patients shows a diurnal variation according to the rhythmus of the metabolic processes.

Möllerström (1947) has presented the alcohol curve of one diabetic alcohol-former, on whom a value of 2.2 $^0/_{00}$ was obtained with Widmark's method at one time of the day, and a value of 1.45 $^0/_{00}$ with the method of Friedemann-Klaas at the same time. Among fasting diabetic patients the results obtained by using Widmark's micromethod were equal to or exceeded 1.5 $^0/_{00}$ in 1 per cent, 0.8 $^0/_{00}$ in 7 per cent, and 0.5 $^0/_{00}$ in 10 per cent of the cases. In another series the subjects were given 160 g of bread, and among them, the respective values was equal to or exceeded 1.5 $^0/_{00}$ in 0.8 per cent, 0.8 $^0/_{00}$ in 9.9 per cent, and 0.5 $^0/_{00}$ in 16 per cent. There was no mention of the presence of ketone bodies in urine. Bjerver *et al.* (1949) have reported that by using Widmark's micromethod, they obtained an average concentration of 0.02 $^0/_{00}$ of alcohol on the blood of diabetic patients, whereas it was respectively 0.01 $^0/_{00}$ in their group of healthy subjects. The highest blood alcohol value observed by them in an abstaining diabetic patient was 0.11 $^0/_{00}$. Alha (1950) has found 0.27 $^0/_{00}$ of oxidizable volatile substances in one case and over 1.0 $^0/_{00}$ in another case of acetonaemic diabetes, by using Widmark's method.

It may be mentioned furthermore that Kohberg (1930) has observed that the basal value of diabetic patients was slightly higher than that of normal subjects, and that Dell'Acqua (1932) in his — admittedly very small — material (4 cases) found an average basal value of 0.043 $^0/_{00}$ in diabetic patients, whereas in healthy subjects the respective value was 0.037 $^0/_{00}$. Schmidt (1937) has made determinations of basal values on four subjects in diabetic coma, also using Widmark's micromethod, and obtained 0.07 $^0/_{00}$ as the highest value, while the basal values of the healthy subjects in his material varied between 0.017 and 0.027 $^0/_{00}$. It is evident that the eventual presence of ketone bodies must be considered, when judging the blood alcohol analyses of diabetic patients. Thus, Widmark (1917) has observed in a severe comatose state that the concentration of ketone bodies alone may rise to 0.07 $^0/_{00}$. Kirk (1942) reports that their concentration may be on such cases as

high as 2—3 ‰. Hartmann (1935), on the other hand, has found lactic acid values up to 0.65 ‰ in diabetic coma.

OWN INVESTIGATIONS

The present material comprises 21 cases of diabetes, of these 13 male and 8 female. The blood alcohol determinations were made on them on 74 blood samples by using Widmark's method in the following way: each patient was subjected to a determination at 7.00 a.m., 15 of them in addition at 9.00 a.m. and 1.00 p.m., and 4 of them at 8.00 a.m. and 11.00 a.m. Furthermore, on 15 patients the determination of the basal value was repeated once more on the following morning. The patients fasted the night preceding the experiment and were given no insulin on the morning of the day of the experiment; they were also left without retarded insulin on the preceding day.

Simultaneously with the basal determination, a blood sugar determination was also made in 66 cases, by using the method of Hagedorn-Jensen, and a qualitative test for urinary ketone bodies was made with Gerhard's and Legal's reactions (Table 5).

The average *basal value of the male diabetic patients was* 0.017 ‰, and of *the female patients* 0.015 ‰. The mean of *the material as a whole was* 0.016 ‰. The values vary between 0.000 and 0.061 ‰. During the course of a morning, the basal values showed some variation, but it was too small to exceed the analytical error. During different days, on the contrary, the values of each subject might have shown differences.

A fall in the blood sugar was observed during the experiment, when repeated analyses were taken, except in a few cases. This fall was probably due to the fasting.

There was no clear correlation between the basal values and the simultaneous blood sugar values of the diabetic patients (Fig. 1).

Table 6 shows the cases as arranged into basal value groups, according to whether the qualitative test for urinary ketone bodies was negative or positive. No definite conclusions can, of course, be made on the basis of the table, because the material shows a very uneven distribution in respect of the urinary tests. However, it is interesting to note that in the majority of cases in which Gerhard's and Legal's tests were negative, the basal value remains below

TABLE 5

ENDOGENOUS ALCOHOL (‰) OF DIABETIC PATIENTS, AS DETERMINED WITH WIDMARK'S MICROMETHOD. BLOOD SUGAR IN MG %, AS DETERMINED WITH THE METHOD OF HAGEDORN-JENSEN, AND THE RESULTS OF GERHARD'S AND LEGAL'S QUALITATIVE TESTS FOR THE URINARY KETONE BODIES (ACETONE AND ACETOACETIC ACID)

	Sex	7.00 a. m.				8.00 a. m.				9.00 a. m.				11.00 a. m.				1.00 p. m.				Next morning 7.00 a. m.			
		Widmark	Blood sugar	Ge	Le	Widmark	Blood sugar	Ge	Le	Widmark	Blood sugar	Ge	Le	Widmark	Blood sugar	Ge	Le	Widmark	Blood sugar	Ge	Le	Widmark	Blood sugar	Ge	Le
V. N.	Male																								
E. M.	,,	0.021	285	—	—					0.015	280	—	—					0.024	244	—	+	0.050	200	—	+
E. S.	,,	0.023	334	—	—					0.029	331	—	—					0.016	296	—	—	0.022	316	—	—
M. A.	,,	0.014	257	—	—					0.025	243	—	—					0.028	207	—	+	0.000	270	—	—
A. O.	,,	0.000	231	—	—					0.000	210	—	—					0.000	168	—	—	0.000	247	—	—
A. R.	,,	0.008	169	—	—					0.006	122	—	—					0.000	128	—	—	0.055	189	—	+
P. T.	,,	0.025	216	—	—	0.022				0.032	250	—	—	0.020				0.035	246	+	+	0.025	248	—	+
M. K.	,,	0.000	284	—	—	0.000				0.004	306	—	—	0.004				0.000	306	—	—	0.029	338	—	+
H. N.	,,	0.000	130	—	—					0.000	162	—	—					0.000	129	—	—	0.000	122	—	—
R. S.	,,	0.018	213	—	+					0.047	209	—	+					0.029	202	—	+	0.022	310	—	+
P. V.	,,	0.027	294	—	+																				
A. J.	,,	0.026	250	+	+																				
K. T.	,,	0.000	310	—	—																				
S. W.	Female	0.061	246	+	+																				
A. L.	,,	0.026	126	—	—					0.014	119	—	—					0.029	120	—	—	0.000	131	—	—
H. K.	,,	0.000	241	—	—					0.000	228	—	—					0.000	228	—	—	0.000	255	—	—
M. R.	,,	0.005	188	—	+					0.017	174	—	+					0.027	166	—	+	0.044	178	—	+
T. J.	,,	0.017	163	—	—					0.023	136	—	—					0.016	108	—	—	0.018	185	—	—
A. L.	,,	0.008	290	—	—	0.004				0.004	277	—	+	0.008				0.004	232	—	+	0.042	230	+	+
A. V.	,,	0.020	343	—	—	0.031				0.017	337	—	+	0.024				0.018	355	—	+	0.038	326	+	+
H. S.	,,	0.025	356	+	+																				
		0.020	342	—	+																				

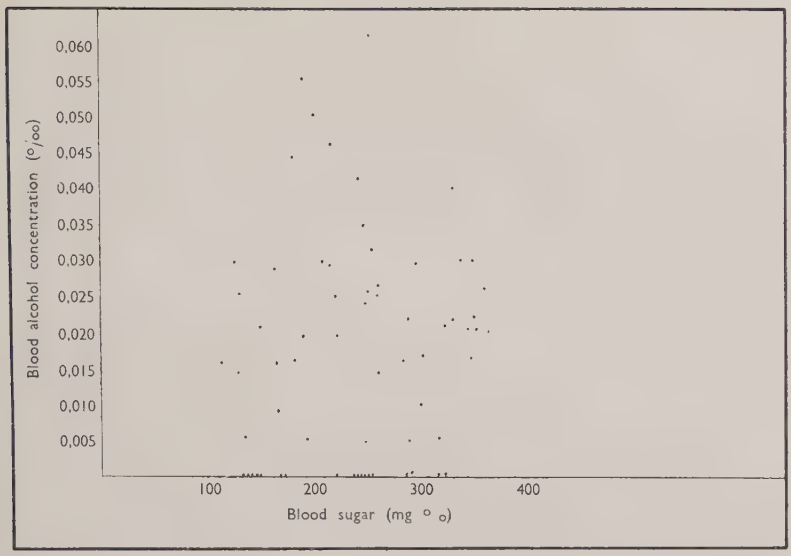

Fig. 1.— The comparison of the blood alcohol (basal values) and the simultaneous blood sugar values of diabetic patients.

TABLE 6

THE RELATION OF THE BASAL VALUES IN THE BLOOD OF DIABETIC PATIENTS AS OBTAINED BY USING WIDMARK'S MICROMETHOD, AND OF THE URINARY KETONE BODIES (GERHARD'S AND LEGAL'S TESTS)

Basal alcohol ‰	Ge− Le−	Ge− Le+	Ge+ Le+	Number of cases
0.000—0.005	19	3		22
0.006—0.010	3			3
0.011—0.015	3			3
0.016—0.020	5	5		10
0.021—0.025	6	3	1	10
0.026—0.030	3	5	1	9
0.031—0.035	1		1	2
0.036—0.040			1	1
0.041—0.045		1	1	2
0.046—0.050		2		2
0.051—0.055		1		1
0.056—0.060				0
0.061—0.065			1	1
Total	40	20	6	66

0.005 $^0/_{00}$, and that in cases with positive results in both Gerhard's and Legal's tests, the basal values vary between 0.021 and 0.045 $^0/_{00}$, except for one case with 0.061 $^0/_{00}$. The comparison of the results would give a different picture, if both groups were numerically equal.

When comparing the basal values of the diabetic patients with those of the normal group, it is observed that the maximum value in each group is about the same, but that the mean is slightly higher in the former group. There was no such case of diabetes in the present material, in whom the basal value as obtained by using Widmark's micromethod would have even approached the lowest statutory limit of blood alcohol.

VIII

CONCENTRATION OF ALCOHOL IN THE BLOOD OF HEALTHY SUBJECTS AFTER AN INGESTION OF ALCOHOL

PREVIOUS STUDIES

The normal route of the access of alcohol into the human body is per os. Alcohol intoxications due to inhalation or to alcohol compresses have been mentioned in literature, but they have no practical importance.

According to the prevailing view, alcohol is absorbed almost completely, partly from the stomach, and partly from the small intestine. To what extent the absorption and particularly its rate is affected by the varying condition of the stomach, is a subject under dispute. Some investigators claim that the absorption occurs more rapidly from an inflamed stomach, perhaps because of the hyperaemia. Alcohol ingested into the stomach of fasting subjects immediately begins to be absorbed. If the solution is ingested within a short time, the absorption is completed in general within less than one hour.

The increase of blood alcohol concentration during the absorption can be followed from the shape of the blood alcohol curve. It shows an initial more or less steep rise, in other words, a more or less rapid absorption. In such subjects, who have used much alcohol, the absorption seems to proceed more rapidly than in subjects unused to alcohol (Schweisheimer 1913, Bernhard and Goldberg 1935, Schmidt 1937). According to the studies of Bernhard and Goldberg (1935) on 18 male alcoholics and on 6 subjects unused to alcohol, the time taken for the maximum of the blood alcohol concentration to be reached was 32 min. in the former group, and 46 min. in the latter, when the subjects were given between 0.44 and

0.79 g of alcohol per kg body weight. They also observed that the more rapid the absorption, the higher the maximum blood concentration attained.

The view presented by Tuovinen (1926, 1930) that dilute solutions of alcohol raise the blood alcohol level more than concentrated drinks do, has gained general acceptance. Alcohol ingested together with, or after food is absorbed more slowly and the blood alcohol concentration remains lower than when alcohol is ingested into an empty stomach (Mellanby 1919, Southgate 1925, Handwerk 1927, Tuovinen 1930, Kriebs 1934, Schmidt 1937, Elbel 1937, etc.). Evidently, some individual factors also modify the rate of absorption.

Simultaneously with the absorption of alcohol from the stomach into the blood vessels, it diffuses over the surrounding tissues and further over the whole body. However, it does not penetrate into the fatty tissue or to the bone (Carpenter 1929). When the absorption of alcohol is reduced to such an extent that its diffusion into the tissues, its combustion, and its possible elimination through the respiratory tract, through sweat and through the kidneys becomes dominant, the blood alcohol curve begins to fall. After a diffusion equilibrium is attained, the curve starts to fall in a linear fashion. As already mentioned, Gréhant (1896) and his supporters claim that before the onset of the gradual fall, the curve shows a plateau phase. However, most of the later investigators have been unable to confirm the existence of such a plateau phase in the majority of their experiments (Widmark 1930—1933, Jungmichel 1933, Schmidt 1937, Elbel 1937, etc.).

The observation, made by Widmark (1932), that the blood alcohol concentration in the elimination phase, *i. e.* after all the alcohol ingested is absorbed, falls at a constant rate, is also at present in accordance with the concepts of most investigators. According to him, the combustion of alcohol in the body is independent of the concentration and of the amount of alcohol ingested. This is indicated by the rectilinear shape of the curve during the elimination phase. Haggard and Greenberg (1934) have made an attempt to exclude any irregularities in the absorption, due to the gastric or intestinal mucosa, by administering alcohol intravenously. In their experiments they arrived at the conclusion that the metabolism of alcohol is an exponential process, the rate of elimination being directly proportional to the blood alcohol concentration. Newman, Lehman

and Cutting (1937) administered from 1 to 6 ml of alcohol per kg body weight to dogs, similarly using the intravenous route; they observed that doubling the dose of alcohol increased the rate of elimination every time by exactly 17 per cent. However, they did not regard their results as conclusive enough to disprove Widmark's theory. Newman (1949), partly also in collaboration with Cutting and Yee (1949), has published results of work made on dogs which confirm the observations of Newman *et al.* (1937). The forensic blood alcohol determination is in most countries still based on Widmark's theories.

Widmark (1932, 1933) expresses the alcohol metabolism of man and animals with the aid of two factors, β and r, which show some individual variation, but are regarded as fairly constant in each subject. *The factor β expresses the rate of the elimination of alcohol, or the fall of blood alcohol concentration in $^0/_{00}$ per unit of time, and the factor r indicates the relation between the amount of alcohol in the body and its concentration in blood.* These factors are applicable if the amount of alcohol is completely absorbed and if the diffusion equilibrium has been attained. Thus, they can be determined only during the elimination phase of the blood alcohol curve.

Widmark (1932) has determined the values of the factors β and r from the blood alcohol curves of men and women, and assessed an average value of β for men at 0.0025, and for women at 0.0026; the values of r were 0.68 and 0.55, respectively.

Some investigators have determined these values for the Swedish, German, and Danish population (Table 7 and 8). For healthy Finnish men, the Blood Alcohol Committee appointed by the Finnish Government has published (1949) the factors β and r after a dose of 0.5 and 1.0 g of alcohol per kg body weight. β had an average value of 0.0025 in the material as a whole; after the dose of 0.5 g it was 0.0020, and after the ingestion of 1.0 g, 0.0031. Because the relation of the rate of the elimination of alcohol and the blood alcohol concentration seems to be, according to this investigation, in disagreement with Widmark's generally accepted theory, Alha (1950) has studied the variation of the constants β and r in men, after the ingestion of varying amounts of alcohol, by administering 0.75, 1.0, or 1.25 g of it per kg body weight; the aim was, among other objects, to study this matter further. According to this — still unpublished — study, Widmark's theory is valid.

TABLE 7

THE CONSTANTS β AND r FOR MEN, ACCORDING TO THE MATERIAL OF SOME INVESTIGATORS

Investigator	Number of cases	β	r
Widmark	20	0.0025	0.68
Abramson and Linde	4	0.0020	0.83
Liljeström and Linde	3	0.0020	0.62
Jungmichel	6	0.0020	0.76
Kriebs	4	0.0018	0.79
Nyman and Palmlöv	7	0.0023	
Bernhard and Goldberg	6	0.0026	0.60
Schmidt	28	0.0027	0.82
Elbel	5	0.0021	0.73
Goldberg	9	0.0021	0.70
Österlind, Åhlén and Wolff	10	0.0020	0.70
The Finnish Blood Alcohol Committee	20	0.0025	0.71
Own cases	19	0.0020	0.72
Total	141		

TABLE 8

THE CONSTANTS β AND r FOR WOMEN, ACCORDING TO THE MATERIAL OF SOME INVESTIGATORS

Investigator	Number of cases	β	r
Widmark	10	0.0026	0.55
Jungmichel	3	0.0020	0.67
Kriebs	19	0.0025	0.62
Elbel	2	0.0020	0.63
Österlind, Åhlén and Wolff	20	0.0023	0.64
Own cases	23	0.0022	0.66
Total	77		

The average value for the constant β of all the male subjects presented in Table 7 is 0.0022. The table indicates the number of the subjects only, and not the number of individual experiments; some investigators may have performed several experiments on the same subject. Further, it includes partly abstainers, partly subjects using alcohol in moderate amounts, without presenting them separately. Alcoholics are not included in the table. The same

remarks concern the female subjects presented in Table 8. Some investigators (Miles 1922, Graf and Flake 1933) consider the alcohol metabolism of alcoholics and abstainers as identical. Bernhard and Goldberg (1935) and Schmidt (1937) have obtained almost identical values for the constants β and r in subjects with high and very low alcohol consumption. Hansen (1925), Jungmichel (1933) and Elbel (1937) have come to the conclusion that an ample consumption of alcohol has a slight enhancing action on the rate of disappearance of alcohol, and thus increases the value of β. Goldberg (1943) has assessed the value of β at 0.0021 in 9 abstainers, at 0.0023 in 16 male subjects with a record of moderate alcohol consumption, and at 0.0026 in 14 male alcoholics.

Similar studies on female subjects have not been carried out to the same extent. Table 8 gives 0.0023 as the mean value of β of the women studied. Kriebs' (1934) material has been included, in spite of the fact that the subjects probably had not been fasting before the alcohol tolerance experiment. Kriebs (1934) forms the conclusion from his 19 female subjects that the elimination of alcohol is retarded in women possessing an ample fatty tissue, who have previously used only small amounts of alcohol, and who were resting during the experiment: thus, their constant β has a low value.

Widmark (1932) explains the small values of r observed in female subjects as depending on the relatively great proportion of fat in the female body. This opinion is supported among others by Graf and Flake (1933), Jungmichel (1933), Elbel (1937), and Hoffmann (1937). Kriebs (1934) has not discovered any correlation between the constant r and the amount of fat in body in his material. However, he makes — with reservation — the conclusion from the female subjects he studied that women possessing a very feminine constitution and plenty of fat have the constant r on an average at 0.54 (from 0.58 to 0.50), women with a feminine constitution but with little of fat on an average at 0.62 (from 0.66 to 0.58), and very thin, masculine women at 0.67 (from 0.74 to 0.60). Jungmichel (1933) also points out that r most often depends on the constitution, having high values in subjects with an asthenic constitution, medium values in athletic types, and low values in pyknic subjects. Elbel (1937) has observed a small r among his material, which comprised 7 subjects, 5 men and 2 women, in a fat, pasty subject, normal r in a slim subject, and a high value of r in a corpulent and tall subject.

Widmark (1932) is of the opinion that no correlation obtains between the constants β and r. Meyer (1935) has made experiments on rabbits, and he has, on the contrary, observed that a rise of r is connected with a fall of β and vice versa. Moreover, he has noted that in the animals r often exceeds unity. He explains this as being caused by anatomical circumstances typical of the rabbit. According to Neymark's (1937) opinion, this observation in rabbits can be explained by the particularly long delay of food in the stomach of rabbits, and thus the assumption of a condition of fasting may not actually be valid. Investigating the interrelations of β and r in dogs, he has arrived at similar results as Meyer (1935), but his opinion is that there is no physiological relationship between them, and the negative correlation coefficient must depend on an error in the calculation of β and r. Also Schmidt (1937) has observed the correlation between β and r in his material.

OWN INVESTIGATIONS

The shape of the alcohol curve. — The present material comprises 19 healthy male and 23 female subjects. In some of the normal cases

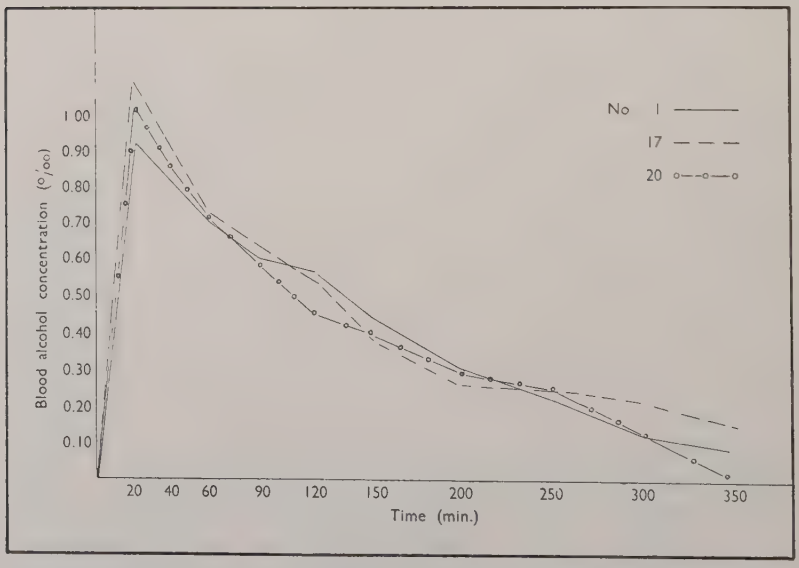

Fig. 2.— Blood alcohol curves with a steep rise, reaching the maximum in a short time.

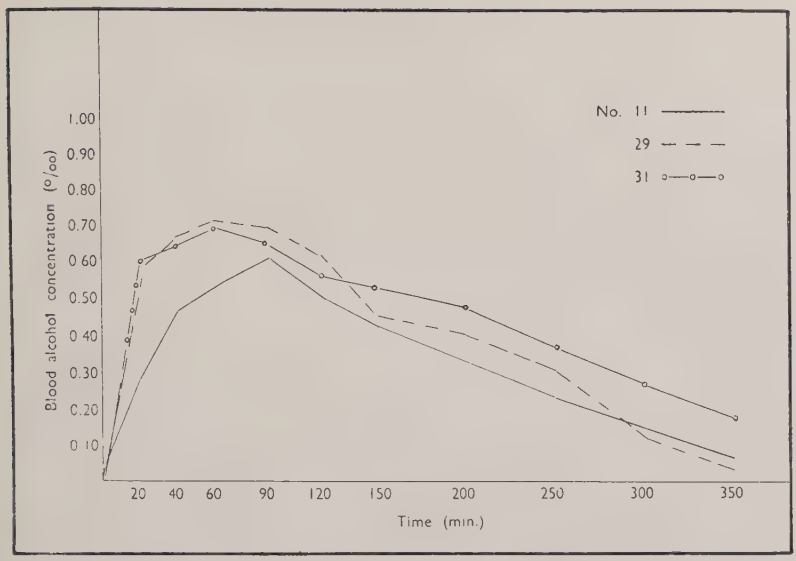

Fig. 3.— Blood alcohol curves with a slow rise, reaching the maximum after a considerable delay.

the blood alcohol curve rose steeply, and the maximum was attained in a short time (Fig. 2), whereas in others the rise was slow and the maximum was attained late (Fig. 3). In some of the curves, there is a fairly early maximum, after that a rather steep fall, followed by a more gradually falling slope (Fig 4). Such curves were observed in 6 of the male subjects and in 5 among the females. The shape of the curve in these subjects may evidently be explained to some extent by a rapid absorption of the alcohol and, at the same time, by a relatively slow diffusion of alcohol into the tissues, for a high maximum of the alcohol curve is most often observed in such cases in which the maximum is attained rapidly. The materials of Jungmichel (1933), Bernhard and Goldberg (1935) and of Schmidt (1937) include several curves of this type.

After an attained maximum, none of the blood alcohol curves of the present material showed a level phase (Gréhant's »plateau»).

It is, however, very difficult to analyse the first phase of the blood alcohol curve. The time elapsing prior to an attained maximum, and the observed maximum concentration, depend very much on the frequency of sampling. The more often the samples are taken, the more accurately the shape of the curve can be pre-

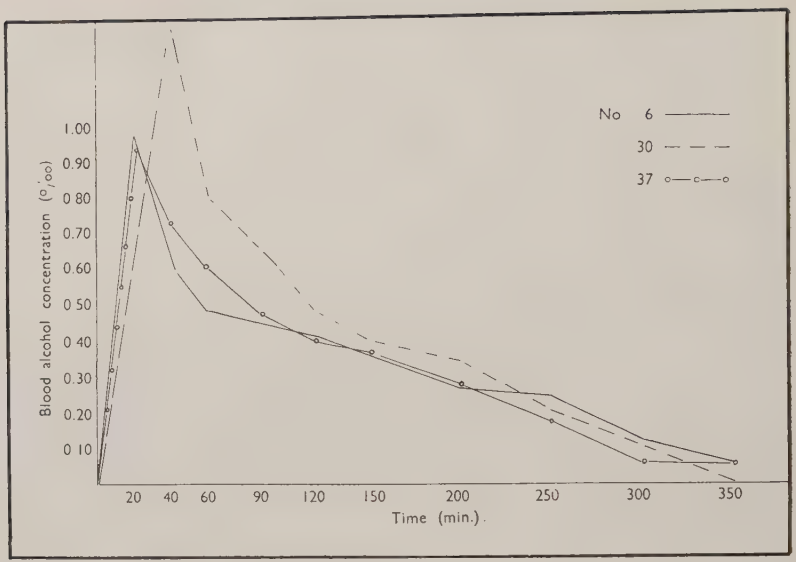

Fig. 4.— A rapidly attained maximum, a steep fall, and finally a more or less gently sloping course of the curve.

sented. The maximum may, of course, be attained on either side of the highest concentration observed, if the interval between the subsequent determinations is long enough. Since it was not the primary aim of the present work to elucidate this problem, the writer contented himself with taking samples every 20 minutes during the first phase, every 30 minutes during the diffusion phase, and every 50 minutes during the elimination phase, which is the most important one for the determination of the constants, as pointed out above. Literature also gives support to this as being a suitable frequency of sampling, particularly for the determination of the constants.

The postabsorptive phase of the cases in general shows a linear fall, and thus the elimination of alcohol occurs at an even rate, which is in agreement with the observations of Mellanby (1919) and Widmark (1932).

The rate of the elimination of alcohol. — The calculation of β is made by employing an equation derived by the method of the least squares:

$$\beta = \frac{\sum (\sum t_v - n\, t_v)\, x_v}{n \sum t_v^2 - (\sum t_v)^2}, \text{ where}$$

t_v = time of observation, as calculated from the administration of the alcohol;

x_v = the concentration of alcohol at the moment t_v;

n = the number of determinations to be taken into account in the calculations. (Only these determinations are considered in calculating the sums $\sum$).

Most of the values of β presented in literature are calculated as per minute, and then the time in the above formula is expressed in minutes. These values vary in general between 0.0011 and 0.0040. A multiplication by 60 gives, of course, the corresponding factor per hour.

The body weight of the healthy subjects of the present material (19 men and 23 women) varied between 40.8 and 80.0 kg, their

TABLE 9

THE RESULTS OF THE HEALTHY MALES

As is customary in the literature, the values of β and r are given with two significant figures. However, the values of b_{60}, $\frac{b_{60}}{p}$ and T are giwen with three significant figures. For the calculation of the latter, more accurate values of β and r were used

No.	Age	Stature cm	Body weight kg	Constitution	β	r	b_{60}	$\frac{b_{60}}{p}$	T
1	23	162.0	55.3	asthenic	0.0023	0.60	4.63	83.7	56.4
2	59	168.0	60.4	asthenic	0.0019	0.71	4.98	82.4	67.6
3	25	173.0	68.8	pyknic	0.0020	0.74	5.98	87.0	80.6
4	25	178.0	67.6	athletic	0.0018	0.79	5.67	83.8	82.0
5	22	175.0	62.4	asthenic	0.0019	0.76	5.27	84.5	73.6
6	16	157.0	40.8	asthenic	0.0015	0.86	3.21	78.7	51.0
7	42	172.0	69.5	athletic	0.0022	0.69	6.26	90.0	79.3
8	41	173.0	80.0	athletic	0.0017	0.77	6.15	76.9	92.2
9	27	176.0	68.3	athletic	0.0017	0.90	6.15	90.1	92.1
10	31	169.0	54.0	asthenic	0.0017	0.83	4.55	84.3	67.6
11	23	181.0	70.0	athletic	0.0021	0.66	5.73	81.8	75.1
12	26	170.0	74.0	athletic	0.0018	0.80	6.09	82.3	90.0
13	29	161.0	68.0	pyknic	0.0024	0.60	5.76	84.7	69.6
14	43	178.0	76.0	athletic	0.0020	0.72	6.49	85.4	87.1
15	21	180.0	76.0	athletic	0.0016	0.86	6.18	81.4	96.0
16	37	163.0	73.0	pyknic	0.0027	0.59	6.93	95.0	78.1
17	40	177.0	64.0	asthenic	0.0023	0.60	5.35	83.6	65.4
18	31	177.5	72.0	athletic	0.0018	0.65	4.97	69.1	71.6
19	23	175.0	69.0	pyknic	0.0024	0.59	5.98	86.7	70.6

TABLE 10

THE RESULTS OF THE HEALTHY FEMALES

No.	Age	Stature cm	Body weight kg	Constitution	β	r	b_{60}	$\frac{b_{60}}{p}$	T
20	52	158.0	64.0	pyknic	0.0025	0.60	5.69	88.9	66.8
21	54	161.0	63.3	pyknic	0.0024	0.63	5.65	89.3	68.0
22	38	162.0	73.0	pyknic	0.0021	0.61	5.70	78.0	73.1
23	42	166.0	57.0	athletic	0.0017	0.73	4.37	76.7	63.6
24	37	163.0	67.4	pyknic	0.0021	0.72	6.18	91.7	79.1
25	44	152.0	42.5	asthenic	0.0020	0.68	3.55	83.6	46.8
26	18	162.5	55.0	athletic	0.0023	0.66	4.97	90.4	60.9
27	36	162.0	51.0	asthenic	0.0022	0.66	4.32	84.8	55.1
28	66	156.0	61.0	pyknic	0.0028	0.55	5.56	91.2	61.1
29	25	153.0	51.0	pyknic	0.0026	0.55	4.41	86.5	50.2
30	43	160.0	52.0	asthenic	0.0025	0.60	4.66	89.7	54.3
31	38	155.0	61.0	pyknic	0.0018	0.62	4.17	68.3	58.8
32	26	161.5	63.0	pyknic	0.0021	0.67	5.40	86.7	69.1
33	32	157.0	52.0	asthenic	0.0023	0.64	4.63	89.0	67.4
34	23	165.0	56.7	athletic	0.0021	0.57	4.04	71.3	52.8
35	24	162.0	56.4	athletic	0.0021	0.65	4.65	82.4	59.8
36	23	158.0	53.3	asthenic	0.0029	0.52	4.85	91.0	51.8
37	31	165.0	54.0	asthenic	0.0019	0.73	4.63	85.7	62.8
38	23	171.0	67.0	athletic	0.0026	0.57	5.91	88.2	67.6
39	29	163.5	65.0	asthenic	0.0019	0.77	5.70	87.6	78.8
40	22	172.0	72.0	athletic	0.0018	0.86	6.71	93.2	95.8
41	22	150.0	50.2	asthenic	0.0022	0.72	4.75	94.6	59.7
42	21	168.5	66.5	athletic	0.0018	0.79	5.59	84.1	80.4

age between 16 and 66 years, the majority being from 20 to 30 years old. The average weight of the men was 66.3 kg, and that of the women 58.9 kg. The majority of the men had previously used alcohol seldom, some were practically abstainers, as were most of the women of the normal group. None of the subjects showed any symptoms of an intoxication during the experiment.

The constant β of the male subjects was on an average $0.00199 \pm \pm 0.00007$, *with a standard deviation* $\sigma = \pm 0.00032$, maximum value 0.0027, and minimum value 0.0015.

The values for women were respectively: mean 0.00220 ± 0.00007, $\sigma = \pm 0.00033$, and range from 0.0029 to 0.0017 (Table 9 and 10). The value of β as obtained in the present material agrees thus with the value obtained by the Blood Alcohol Committee (1949) by using 0.5 g of alcohol per kg body weight. The value of β as obtained on women was slightly higher than that of the men, as generally observed.

TABLE 11

THE RESULTS OF THE OBESITY GROUP

A case of asthenia in brackets

No.	Age	Stature cm	Body weight kg	Constitution	β	r	b_{60}	$\frac{b_{60}}{p}$	T
43	29	171.0	108.5	athletic	0.0017	0.63	6.93	63.9	103.0
44	39	161.0	155.0	pyknic	0.0020	0.42	7.83	50.5	104.8
45	39	157.0	95.0	pyknic	0.0022	0.54	6.80	71.5	85.2
(125	29	146.0	38.9	asthenic	0.0017	0.91	3.62	92.9	53.4)

No correlation was observed in the present material between body weight, and the value of β. Admittedly, Table 11, which includes 3 female subjects with a considerable overweight, shows two cases, No. 43 and 44, with a β slightly lower than the average value for women. However, no conclusions can be drawn from the results of so few cases.

For comparison, Table 12 shows the distribution of β according to its numerical value in the material of Widmark (1932), Österlind *et al.* (1944) and in the material of the present work, both for male and female subjects.

TABLE 12

THE DISTRIBUTION OF THE CONSTANT β FOR MEN AND WOMEN ARRANGED BY NUMERICAL VALUE; THE RESULTS OF SOME INVESTIGATORS

β	Men				Women			
	Widmark	Österlind, Åhlén and Wolff	Own cases	Total	Widmark	Österlind, Åhlén and Wolff	Own cases	Total
0.0015—0.0020	5	6	12	23	1	2	7	10
0.0021—0.0025	7	4	6	17	2	12	12	26
0.0026—0.0030	6	0	1	7	6	6	4	16
0.0031—0.0035	1	0	0	1	1	0	0	1
0.0036—0.0040	1	0	0	1	0	0	0	0
Total	20	10	19	49	10	20	23	53

The diffusion of alcohol from blood into tissues. — For the determination of the constant r, a value is needed which indicates the theoretical alcohol concentration to be expected after a complete absorption of the alcohol ingested and during an attained diffusion equilibrium, when no elimination of the alcohol has occurred. This value is denoted by c_0. Starting from the assumption that the rate of the elimination of alcohol is independent of its concentration, c_0 can be calculated from that part of the blood alcohol curve which represents the time after an attained diffusion equilibrium, by using the following equation:

$$c_0 = \frac{\sum(\sum t_v^2 - t_v \sum t_v) x_v}{n \sum t_v^2 - (\sum t_v)^2}$$

It is known that the amount of alcohol in the human body at any moment is the product of the alcohol concentration in the body and the weight of the body, and, on the other hand, that the concentration of alcohol in the body is the product of the blood alcohol concentration and r (r = body alcohol concentration/blood alcohol concentration), or, as an equation:

$A = c_0 p r; r = \frac{A}{c_0 p}$, where

A = the amount of alcohol consumed, and

p = body weight kg.

The values of r as mentioned in literature vary most often between 0.50 and 0.85.

The mean value of r for the men of the normal material was 0.72 $\pm$0.023, *with a standard deviation* $\sigma = \pm 0.102$, *the highest value* 0.90, *and the lowest* 0.59 (Table 9). *The values for female subjects were respectively: mean* 0.66 $\pm$0.018, $\sigma = \pm 0.085$, *and range from* 0.86 *to* 0.52 (Table 10). The values are higher than those of Widmark (1932), but they are approximately the same for men as the average value shows in Table 7. The value of r obtained by the Blood Alcohol Committee (1949) for the Finnish male population is also almost identical with the result of the present study. Some of the previous investigators, such as Abramson and Linde (1930), Kriebs (1934), and Schmidt (1937) have observed much higher values of r than mentioned in the more recent literature. It is known that the concentration of alcohol in blood following an ingestion of alcohol after a meal is

TABLE 13

THE DISTRIBUTION OF THE CONSTANT r ACCORDING TO ITS NUMERICAL VALUE; THE RESULTS OF SOME INVESTIGATORS

r	Men				Women			
	Widmark	Österlind et al.	Own cases	Total	Widmark	Österlind et al.	Own cases	Total
0.46—0.50	0	0	0	0	2	1	0	3
0.51—0.55	1	0	0	1	3	1	3	7
0.56—0.60	5	1	5	11	4	4	4	12
0.61—0.65	3	2	1	6	1	6	5	12
0.66—0.70	3	3	2	8	0	4	4	8
0.71—0.75	5	1	3	9	0	4	4	8
0.76—0.80	2	2	4	8	0	0	2	2
0.81—0.85	0	1	1	2	0	0	0	0
0.86—0.90	1	0	3	4	0	0	1	1
0.91—0.95	0	0	0	0	0	0	0	0
Total	20	10	19	49	10	20	23	53

lower than the concentration as produced by the same amount of alcohol ingested on an empty stomach. In such cases the blood alcohol curve is low and flat, and the value of r becomes high. A high alcohol curve with a steep fall again gives a low value of r.

In the group of the female subjects, the value of r was slightly higher than the values obtained by previous investigators. As compared with the value of r in the male group it is distinctly lower, but the difference is not quite so great as that generally mentioned in literature (Table 7 and 8). Table 13 shows a comparison of the numerical values of r as obtained by Widmark (1932), by Österlind, *et al.* (1944), and by the writer.

In the group of healthy subjects, there seems to obtain a correlation between β *and* r (Table 14 and Fig. 5). While r increases, β seems to decrease, and vice versa. Admittedly, the variation of the values of β occurs within rather narrow limits among the subjects, between 0.0015 and 0.0029, the majority having values between 0.0017 and 0.0025; thus, it is perhaps venturesome to draw any definite conclusion on the basis of these experiments.

In addition to the group of healthy subjects blood alcohol studies were also made on three females with a body weight considerably exceeding the average weight of the group of healthy female subjects

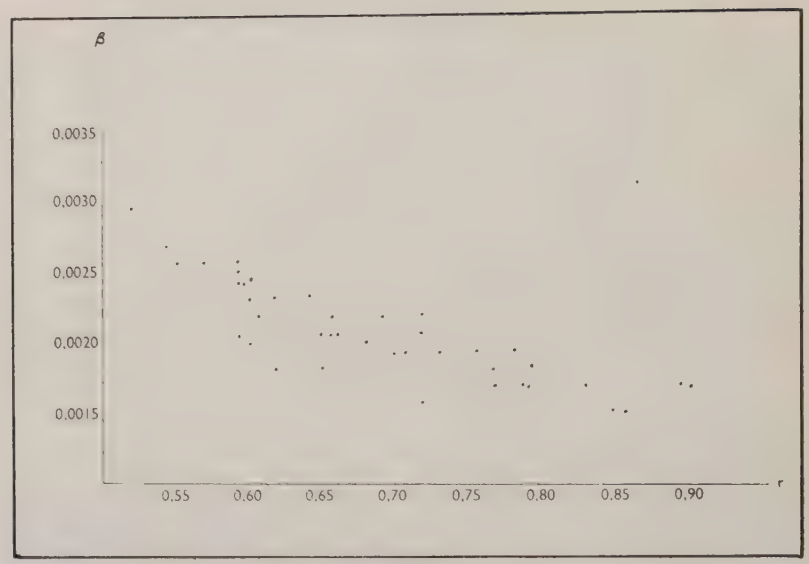

Fig. 5.— The relation of the values of the constants β and r among all the healthy subjects.

(Table 11). None of these cases showed a negative correlation between β and r. In two cases the value of r was considerably lower and even in the third case distinctly lower than the average value for women, and also β was correspondingly lower than the mean of the female normal group, although this difference was smaller.

No correlation was observed in the material of the present work between body weight and the constant r (Fig. 6 and Table 15). Still, Table 11 shows that the subjects with a high body weight have low values of r, even if the lowest values of r do not coincide with the highest

TABLE 14

THE RELATION OF THE NUMERICAL VALUES OF THE CONSTANTS β AND r OF ALL THE HEALTHY SUBJECTS OF THE MATERIAL

β	0.51—0.55	0.56—0.60	0.61—0.65	0.66—0.70	0.71—0.75	0.76—0.80	0.81—0.85	0.86—
0.0015—0.0020	—	—	2	1	5	6	1	4
0.0021—0.0025	—	7	4	5	2	—	—	—
0.0026—0.0030	3	2	—	—	—	—	—	—
Total	3	9	6	6	7	6	1	4

TABLE 15

THE RELATION OF THE BODY WEIGHT (p) AND THE CONSTANT r OF ALL THE HEALTHY SUBJECTS IN THE MATERIAL

p	0.51–0.55	0.56–0.60	0.61–0.65	0.66–0.70	0.71–0.75	0.76–0.80	0.81–0.85	0.86–0.90	Total
-45.0	—	—	—	1	—	—	—	1	2
-50.0	—	—	—	—	1	—	—	—	1
-55.0	2	2	1	2	1	—	1	—	9
-60.0	—	1	1	—	2	—	—	—	4
-65.0	1	2	2	1	—	2	—	—	8
-70.0	—	3	—	2	2	2	—	1	10
-75.0	—	1	2	—	—	1	—	1	5
-80.0	—	—	—	—	1	1	—	1	3
Total	3	9	6	6	7	6	1	4	42

body weight. For comparison, accepted values of *r* for subjects with low body weight are also included in the table. An assessment of *r* simply on account of body weight, as is often done in published work, leads to erroneous results. A knowledge of the stature, of the skeletal growth, of shoulder breadth, and even of the shape of the jaw, together with body weight, gives a better picture of the

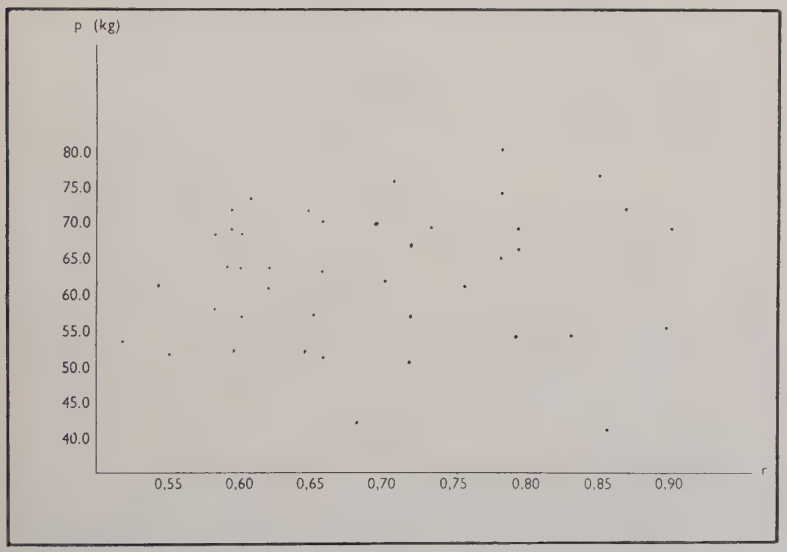

Fig. 6.—The relation of the body weight and the constant r among all the healthy subjects.

constitutional type of the subject. Paying attention to these factors, an attempt was made to distribute the subjects among the various constitutional types. According to Table 9 and Table 10 the value of r in the whole material was smaller in pyknic subjects than in asthenic or athletic subjects. The value of the constant r was in general high in the athletic subjects.

The ability to metabolize alcohol. — By utilizing the constants β and r it can be calculated *e.g., how many grams of alcohol a subject is able to metabolize per unit time. This amount, which is denoted by b,* is obtained from the equation:

$$b = p\, r\, \beta$$

Further, this may be expressed as *calculated per hour,* and then the equation becomes:

$$b_{60} = 60\, p\, r\, \beta$$

This varies between 4 and 11 g.

As can be seen from the equation, the value of b_{60} varies with the body weight of the subject. *Dividing b_{60} by the body weight in kg one arrives at the ability of the subject to metabolize alcohol as expressed in grams per kg body weight.* The result is expressed in mg. This value, b_{60}/p, is thus a more expressive indicator of the subject's ability to metabolize alcohol.

Starting from the accepted condition that the human body always oxidizes a constant amount of alcohol per unit time, the amount of alcohol ingested (A grams) may at any moment be conversely calculated from the blood alcohol concentration as determined at any moment after an attained diffusion equilibrium, if it is fully absorbed. This is determined by using the equation $A = c_0\, p\, r$. When the value of c_0, which is $c_t + \beta t$, is placed into the equation, the following form is obtained:

$A = (c_t + \beta t)\, p\, r$, where
c_t = the concentration of alcohol as observed at a certain time;
t = time in minutes elapsed since the ingestion of alcohol;
p = body weight.

By employing this equation one is able to check the amount of alcohol reported as having been ingested, by determining the concentration of alcohol in blood, presuming that the body weight and the maximum, minimum, and average values of the constants β and r are known in the population.

According to Table 9, *a healthy man is able to metabolize on an average* 5.60 *g* ± 0.20, *with a standard deviation* $\sigma = \pm 0.86$, *of alcohol per hour, and a woman* 5.05 g ± 0.16, *with a standard deviation* $\sigma = \pm 0.78$ (Table 10). The value of b_{60} for men is somewhat lower than that mentioned in literature, but the values for women are about the same (Table 16). However, the value of b_{60} depends primarily and decisively on the body weight of the subject, as may be noted from the equation, and thus the values observed in different materials are not quite comparable. However, the values obtained in the present work agree reasonably well with those of previous investigators, if the effect of body weight is duly considered. As seen in Table 11, very corpulent women may have a value of b_{60}, even considerably exceeding the mean value for men. As the above value depends so closely on body weight, the ability to *metabolize alcohol* was also *determined per kg body weight per hour. Among the men* of the material, this value — 83.8 *mg* ± 1.2, *with a standard deviation* $\sigma = \pm 5.4$ — is also smaller than that mentioned in literature. *The value of* b_{60}/p *for women was* 85.7 *mg* ± 1.4, *with a standard deviation*

TABLE 16

THE ABILITY TO METABOLIZE ALCOHOL, ACCORDING TO THE MATERIAL OF SOME INVESTIGATORS

Investigator	Average body weight kg	b_{60}	$\frac{b_{60}}{p}$	Number of cases
		Men		
Widmark	—	7.3	98.0	20
Jungmichel	75.4	6.7	92.0	6
Kriebs	71.5	6.1	86.5	4
Bernhard and Goldberg	—	6.3	93.0	6
Elbel	72.6	6.6	91.0	5
Goldberg	—	—	96.6	—
Österlind, Åhlèn and Wolff	74.0	6.0	81.3	10
Own cases	66.3	5.6	83.8	19
		Women		
Widmark	—	5.3	86.0	10
Jungmichel	56.6	4.6	79.0	3
Kriebs	60.2	5.8	96.2	19
Elbel	55.0	—	75.0	2
Österlind, Åhlèn and Wolff	60.0	5.3	88.8	20
Own cases	58.3	5.0	85.7	23

$\sigma = \pm 6.7$. Goldberg (1943) has observed that such subjects who have consumed great amounts of alcohol have a slightly higher ability to metabolize alcohol than those who have used it less or abstained from it. His value for b_{60}/p was 87.9 mg in abstainers, 95.5 mg in subjects with the record of a moderate alcohol consumption, and 109.6 mg in alcoholics. Each group consisted of 9 subjects.

The alcohol consumption tolerance. — The human tolerance to alcohol consumption is known to vary greatly. A similar amount of alcohol gives an individually varying blood alcohol concentration. Widmark (1932, 1933) has called *the amount of alcohol that after complete absorption* 5 *hours after the ingestion gives a blood concentration of* 1 $^0/_{00}$ *of alcohol, the alcohol consumption tolerance* (T). This may be calculated from the equation:

$$A = (c_t + \beta t)\, p\, r,$$

by placing there the values $c_t = 1$ and $t = 300$; then the equation becomes:

$$T = (1 + 300\ \beta)\, p\, r$$

This value was higher *in the male group*, 76.1 $g \pm 2.8$, *with a standard*

TABLE 17

THE BLOOD ALCOHOL CONCENTRATION ($^0/_{00}$) OF HEALTHY MALES

No.	Time									
	20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
1	0.92	0.81	0.70	0.60	0.56	0.45	0.31	0.22	0.13	0.09
2	0.56	0.72	0.64	0.53	0.47	0.34	0.32	0.24	0.13	0.03
3	0.59	0.76	0.60	0.55	0.40	0.34	0.24	0.20	0.09	0.02
4	0.55	0.74	0.62	0.44	0.39	0.30	0.27	0.21	0.14	0.00
5	0.32	0.59	0.57	0.55	0.41	0.32	0.27	0.17	0.14	0.02
6	0.91	0.58	0.47	0.42	0.40	0.35	0.25	0.23	0.11	0.06
7	0.64	0.61	0.59	0.55	0.48	0.42	0.28	0.16	0.03	0.00
8	0.47	0.71	0.52	0.51	0.45	0.36	0.32	0.24	0.14	0.01
9	0.36	0.37	0.61	0.46	0.33	0.28	0.21	0.13	0.04	0.00
10	0.49	0.62	0.54	0.44	0.38	0.33	0.23	0.22	0.11	0.00
11	0.27	0.45	0.52	0.61	0.50	0.42	0.33	0.22	0.13	0.04
12	0.44	0.46	0.47	0.51	0.44	0.31	0.31	0.22	0.12	0.00
13	0.68	0.73	0.67	0.63	0.56	0.48	0.38	0.25	0.12	0.00
14	0.61	0.63	0.59	0.57	0.48	0.39	0.26	0.15	0.11	0.03
15	0.64	0.66	0.55	0.47	0.33	0.29	0.24	0.22	0.17	0.00
16	0.47	0.68	0.87	0.58	0.50	0.48	0.41	0.14	0.05	0.00
17	1.08	0.90	0.71	0.60	0.52	0.36	0.23	0.22	0.19	0.12
18	0.43	0.65	0.81	0.57	0.57	0.50	0.47	0.36	0.22	0.12
19	0.56	0.71	0.71	0.68	0.51	0.49	0.36	0.20	0.08	0.04

TABLE 18

THE BLOOD ALCOHOL CONCENTRATION (‰) OF HEALTHY FEMALES

No.	Time									
	20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
20	1.00	0.84	0.74	0.58	0.45	0.40	0.29	0.25	0.12	0.00
21	0.53	0.75	0.66	0.62	0.51	0.40	0.34	0.16	0.08	0.00
22	0.57	0.57	0.65	0.60	0.56	0.48	0.44	0.35	0.12	0.06
23	0.83	0.76	0.59	0.50	0.41	0.34	0.27	0.23	0.18	0.15
24	0.81	0.75	0.61	0.50	0.36	0.27	0.22	0.11	0.09	0.05
25	0.75	0.65	0.61	0.53	0.51	0.42	0.31	0.25	0.13	0.00
26	0.45	0.48	0.61	0.46	0.40	0.31	0.13	0.06	0.01	0.00
27	0.83	0.76	0.63	0.56	0.47	0.36	0.30	0.29	0.13	0.00
28	0.49	0.53	0.62	0.75	0.67	0.48	0.31	0.13	0.09	0.00
29	0.58	0.66	0.71	0.69	0.61	0.44	0.40	0.29	0.09	0.00
30	0.53	1.21	0.79	0.63	0.47	0.39	0.33	0.20	0.10	0.00
31	0.59	0.64	0.69	0.65	0.55	0.53	0.47	0.36	0.25	0.15
32	0.52	0.57	0.74	0.59	0.56	0.46	0.22	0.19	0.10	0.04
33	0.76	0.84	0.70	0.57	0.52	0.40	0.35	0.24	0.10	0.00
34	0.55	0.78	0.86	0.74	0.64	0.49	0.44	0.34	0.26	0.16
35	0.52	0.72	0.60	0.57	0.47	0.45	0.37	0.25	0.06	0.04
36	0.95	1.08	0.82	0.79	0.53	0.40	0.38	0.18	0.13	0.06
37	0.94	0.67	0.59	0.46	0.38	0.36	0.27	0.18	0.06	0.06
38	0.66	0.73	0.85	0.64	0.62	0.54	0.31	0.14	0.09	0.05
39	0.49	0.53	0.63	0.52	0.42	0.34	0.22	0.17	0.10	0.00
40	0.41	0.55	0.64	0.47	0.41	0.22	0.20	0.11	0.02	0.00
41	0.28	0.59	0.65	0.60	0.45	0.31	0.19	0.10	0.04	0.00
42	0.60	0.73	0.61	0.54	0.39	0.26	0.20	0.16	0.13	0.08
THE BLOOD ALCOHOL CONCENTRATION IN CASES OF OBESITY The values for a case of asthenia in brackets										
43	1.00	0.84	0.76	0.66	0.59	0.56	0.48	0.45	0.36	0.25
44	0.54	0.96	1.22	0.95	0.95	0.95	0.78	0.74	0.53	0.45
45	0.82	1.07	0.82	0.74	0.62	0.57	0.51	0.35	0.34	0.11
(125	0.49	0.57	0.47	0.42	0.35	0.31	0.24	0.14	0.09	0.01)

deviation $\sigma = \pm 12.2$, *than in the women,* 64.5 *g* $\pm$ 2.4, *with a standard deviation* $\sigma = \pm 11.5$.

The values of T for the men of the present material are much lower than those obtained by Schmidt (1937), who observed values generally exceeding 100 g. Also T depends on the body weight and the magnitude of r, both of which were higher in Schmidt's (1937) material than in the present writer's group. The high value of r attained by him is probably explained to a great extent by an ingestion of alcohol with food or immediately after it. He himself regards the consumption tolerance of his material as surprisingly high. On the other hand, some of the male subjects in the present

material were relatively small, one of them, a youth of 16 years, weighing 40.8 kg. These tend to reduce the mean value of T, perhaps unduly much.

The blood alcohol concentration of the men and women of the writer's normal material and of obese women are shown in Table 17 and Table 18.

IX

CONCENTRATION OF ALCOHOL IN THE BLOOD IN SOME DISEASES AFTER AN INGESTION OF ALCOHOL

NEUROCIRCULATORY ASTHENIA OR DYSTONIA (NCA)

Under war-time conditions, cases of neurocirculatory asthenia (NCA) are observed fairly often. Service at the front facilitates the appearance of this disease which evidently depends primarily on constitutional factors. Mental tension, physical strain and infection occur almost without exception in the history of these patients. All these factors fill the everyday life of the soldier. For good reasons, this disease has been called *e.g.* Soldier's Heart (DeGraff 1947), as a patient suffering from NCA generally comes to a doctor or to a hospital as a suspected cardiac case. Also the hectic and insecure life of postwar periods, and probably also the rhythm imposed by the rapidly advancing technical age, all these prepare the ground for the development and outbreak of this disease. The patients affected with NCA are in the main relatively young men with a robust physique, and even athletes are among them (Brummer 1945, Adlercreutz 1946). According to an older view, the persons affected had an asthenic constitution.

As mentioned above, cardiac symptoms are prevalent in this disease (Kalaja 1944, Brummer 1945, 1946, Christensen 1945, Adlercreutz 1946, De Graff 1947). The patient has palpitations and feels acute pain or ache in the region of the apex of heart. Intense fatigue, in particular the rapid fatigability of muscles, dyspnea, often independent of exertion, vertigo and headache are also dominant symptoms. Many of the patients sweat profusely, specially from the armpit and on the palms, experience numbness and pricking in the hands, particularly during the night, and some suffer from gastro-intestinal

disturbances, notably from diarrhea which often occurs at some exciting, important moment. The NCA patients in general report a low tolerance towards various poisons, as tobacco, alcohol, and even coffee. After having taken alcohol, they often find it difficult to get to sleep, the heart beats fast, and they experience unusually severe symptoms of hangover even after relatively small amounts of alcohol. They do not like hot baths or the Finnish steam bath, ("Sauna"), as they know that they will easily have palpitations, giddiness and headache afterwards.

An objective examination reveals very little. It is important to observe pulse rate and blood pressure both in recumbent and in standing position, for most NCA patients get slight tachycardia on rising, and the blood pressure increases slightly (Adlercreutz 1946, Kalaja 1947). No reliable auscultatory or *X*-ray findings which would be typical of NCA can be observed in the heart. According to some investigators, the electrocardiogram shows no deviation from normal. Brummer (1945) and Kalaja (1947) have often observed a lowered *T* in an electrocardiogram taken in the standing position, and Vesa and Noro (1945) have observed even a negative *T*, which on exercise gives way to a positive wave, contrary to the finding in a true coronary insufficiency.

The diagnosis of neurocirculatory dystonia is thus made by relying mainly on the case history. For the differential diagnosis, in particular organic cardiac lesions and the overactivity of the thyroid are to be considered, but an accurate clinical examination excludes these possibilities.

The writer's material of NCA comprises 17 patients, 11 men and 6 women. The mean weight of the men was 67.7 and that of the women 59.5 kg (Table 19). Among both, the athletic and the asthenic constitutions are represented, and among the women there were also patients of the pyknic type. Fig. 7 shows a few blood alcohol curves of the NCA patients, after an ingestion of alcohol. The absorption in general occurs rapidly, and the maximum is reached within a fairly short span. After this, the curve shows an even slope, which, however, is generally more gentle than in healthy subjects. The elimination of alcohol seems to be slower in the dystonic patients than in the normal material. Thus, the values of β are as a rule rather low. Eight of the 11 male subjects had a β within the range of 0.0012 to

TABLE 19

THE RESULTS OF THE CASES OF NEUROCIRCULATORY ASTHENIA

No.	Age	Stature cm	Body weight kg	Constitution	β	r	b_{60}	$\frac{b_{60}}{p}$	T
				Male					
46	29	177.5	61.4	asthenic	0.0015	0.89	4.78	77.8	78.7
47	16	175.0	61.8	asthenic	0.0019	0.68	4.70	76.1	65.5
48	31	186.0	69.0	athletic	0.0015	0.87	5.27	76.3	86.3
50	34	172.0	73.6	pyknic	0.0016	0.68	4.66	63.4	73.0
51	27	172.0	67.0	athletic	0.0013	0.90	4.58	68.4	83.0
53	20	168.5	53.0	asthenic	0.0014	0.81	3.66	69.1	61.0
57	30	172.0	70.5	athletic	0.0015	0.70	4.43	62.9	71.3
58	34	175.0	90.0	pyknic	0.0021	0.59	6.85	76.1	87.3
59	22	181.0	63.0	athletic	0.0014	0.79	4.13	65.5	70.2
60	22	159.0	61.0	pyknic	0.0018	0.69	4.48	73.4	64.5
61	29	179.0	75.0	athletic	0.0013	0.80	4.67	62.2	83.7
				Female					
49	37	166.0	65.9	athletic	0.0017	0.67	4.60	69.8	67.4
52	26	161.0	58.0	pyknic	0.0021	0.53	3.97	68.5	50.8
54	41	150.0	59.0	pyknic	0.0020	0.74	5.16	87.5	69.4
55	37	163.5	49.0	asthenic	0.0021	0.65	3.92	80.1	51.5
56	37	160.0	71.0	pyknic	0.0022	0.54	5.11	72.0	64.0
62	34	168.0	54.0	athletic	0.0013	0.93	3.91	72.4	69.8

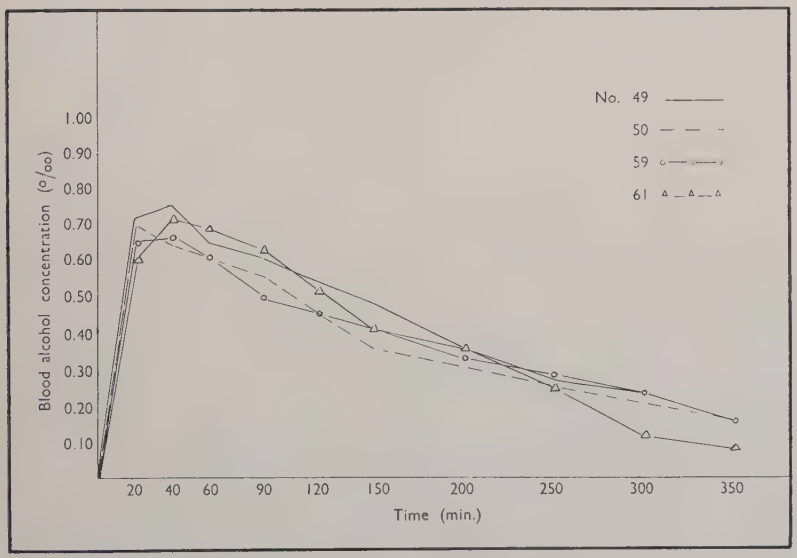

Fig. 7.— Blood alcohol curves of some patients suffering from neurocirculatory asthenia or dystonia.

TABLE 20

THE DISTRIBUTION OF THE CONSTANTS β AND r IN THE GROUP OF NEUROCIRCULATORY ASTHENIA, ARRANGED ACCORDING TO THEIR NUMERICAL VALUE

β	Males	Females
0.0012—0.00014	4	1
0.0015—0.00017	4	1
0.0018—0.00020	2	1
0.0021—0.00023	1	3
> 0.0023	0	0
Total	11	6
r		
0.50—0.55	0	2
0.56—0.60	1	0
0.61—0.65	0	1
0.66—0.70	4	1
0.71—0.75	0	1
0.76—0.80	2	0
0.81—0.85	1	0
0.86—0.90	3	0
> 0.90	0	1
Total	11	6

0.0017 (Table 20). The mean value *for men is* 0.00157 ± 0.00008, *and the standard deviation* $\sigma = \pm 0.00026$. *The* β *of the female subjects* was slightly higher, but their mean value remains lower than the average for healthy women, too; it was 0.00190 ± 0.00014, *with* $\sigma = \pm 0.00034$ (Table 37).

When judging the difference of the average values of the metabolic rate of alcohol (β) in patients suffering from NCA and in healthy subjects, on the other hand, it must be noted that although β is generally regarded as constant in each individual, it may, according to some investigators, vary somewhat even in one and the same subject. Thus Widmark (1933) himself and Meyer (1935) have noted variations of β in individual dogs. However, Widmark (1935), similarly on account of experiments on dogs, draws the conclusion that β is an individual and constitutional factor, which may vary only within narrow limits. Bernhard and Goldberg (1934) have made the independent determinations of β on each of 9 subjects; in one of them they observed a variation of 0.0014, in two 0.0004, and in five 0.0002 in the value of β. In one of the subjects both determinations gave an identical value for β. Schmidt (1937) has

made a similar experiment on 9 subjects, by administering 1.0 g of alcohol per kg body weight; he observed a difference of 0.0001 in one of the subjects, 0.0003 in 3, and 0.0004 in another. Four of them showed identical values of β on both occasions. When administering 0.5 g of alcohol per kg body weight he noted no definite variation in β, except in one case. He himself discards this case as erroneous.

Although the value of β may thus vary even in one and the same individual, the difference obtained between the NCA patients and the healthy subjects of this material is mostly greater than the variations observed by the above authors in the same individual; thus, it may be concluded that the metabolism of alcohol is in fact retarded in NCA patients, particularly if it is considered that the constant β varies in the dystonia material as a whole within rather narrow limits. (See the statistical analysis of the results.)

The values of r for the men were again slightly higher than those obtained in the normal group. Thus, the average value of r is 0.76 ± 0.031, $\sigma = \pm 0.102$. However, the value of r has been shown to vary quite easily even in the same subject, and it is dependent on many individual factors, *e.g.* on the constitution. It is difficult to judge whether the diffusion of alcohol from blood into the tissues is affected by the eventual abnormal distribution of blood in dystonic patients. The mean value of *r of the female NCA patients* and healthy women is almost identical, 0.68 ± 0.061, $\sigma = \pm 0.148$. This group comprises, in addition to asthenic females, also two subjects with a pyknic constitution (Table 19, No. 52 and No. 56), whose r is lower than normal.

The ability to metabolize alcohol per hour as indicated by b_{60} is lower both in the men and women of this group than in healthy subjects, respectively. *In the male patients, it was* 4.75 $g \pm 0.24$, $\sigma = \pm 0.80$, *and in the females* 4.45 $g \pm 0.24$, $\sigma = 0.59$.

The metabolic rate of alcohol for the men of this group was 70.1 *mg* $\pm$ 1.8, $\sigma = \pm 6.0$, *as expressed per hour and kg body weight; for the women it was* 75.1 *mg* $\pm$ 2.9, $\sigma = \pm 7.3$ (Table 19 and 37).

The average value for *the alcohol consumption tolerance* (T) *in the male NCA patients* was almost the same as in the control material, *i. e.* 75.0 $g \pm 2.8$, $\sigma = \pm 9.3$. The body weight of the NCA cases was more evenly distributed than that in the group of healthy subjects, and moreover, r was greater in the former group; these

factors have a decisive influence on the value of T. For these reasons T has only theoretical interest, and it is the writer's opinion that no valid conclusions can be drawn from the observed values. The mean value of T *for the female patients* was also practically the same as in the normal group, *i.e.* 62.2 $g \pm 3.6$, $\sigma = \pm 8.8$.

Table 21 shows the blood alcohol concentrations of the subjects of the NCA group.

ACUTE HEPATITIS

The mean body weight of the members of this group, both of the men (8), 66.9 kg, and of women (11), 56.7 kg, was almost identical with that of the control group. The blood alcohol curve after an ingestion of alcohol resembles, in the first or resorption and diffusion phase, the curves obtained with normal subjects, and as shown in Fig. 4. The rise is generally steep, the absorption proceeds rapidly, and the maximum concentration of alcohol is then fairly high. After the maximum is attained, a steep fall ensues, and the curve falls rapidly to low values. At this stage the alcohol curve of a hepatitis patient seems to assume a different shape than that of

TABLE 21

THE BLOOD ALCOHOL CONCENTRATION (‰) IN THE CASES OF NEUROCIRCULATORY ASTHENIA

No.	Sex	Time									
		20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
46	Male	0.24	0.33	0.47	0.45	0.40	0.33	0.24	0.16	0.13	0.08
47	»	0.56	0.75	0.65	0.57	0.48	0.45	0.36	0.33	0.13	0.09
48	»	0.59	0.71	0.55	0.43	0.43	0.32	0.20	0.19	0.14	0.12
49	Female	0.72	0.76	0.65	0.61	0.53	0.49	0.36	0.27	0.24	0.17
50	Male	0.70	0.64	0.61	0.55	0.44	0.36	0.31	0.25	0.20	0.17
51	»	0.64	0.58	0.51	0.45	0.36	0.31	0.23	0.22	0.21	0.16
52	Female	0.70	0.96	0.90	0.77	0.71	0.47	0.44	0.40	0.34	0.23
53	Male	0.20	0.33	0.49	0.47	0.45	0.38	0.36	0.31	0.18	0.10
54	Female	0.46	0.66	0.81	0.60	0.45	0.31	0.20	0.16	0.08	0.06
55	»	0.79	0.76	0.65	0.56	0.54	0.42	0.33	0.16	0.14	0.15
56	»	0.58	0.94	0.88	0.79	0.55	0.55	0.39	0.39	0.28	0.19
57	Male	0.27	0.40	0.68	0.61	0.56	0.43	0.43	0.30	0.30	0.20
58	»	1.10	0.93	0.76	0.65	0.49	0.37	0.31	0.31	0.29	0.15
59	»	0.64	0.65	0.61	0.49	0.45	0.41	0.33	0.28	0.24	0.16
60	»	0.36	0.36	0.61	0.55	0.53	0.46	0.38	0.27	0.17	0.12
61	»	0.60	0.72	0.68	0.63	0.52	0.41	.036	0.25	0.12	0.08
62	Female	0.26	0.55	0.46	0.42	0.38	0.33	0.27	0.25	0.13	0.08

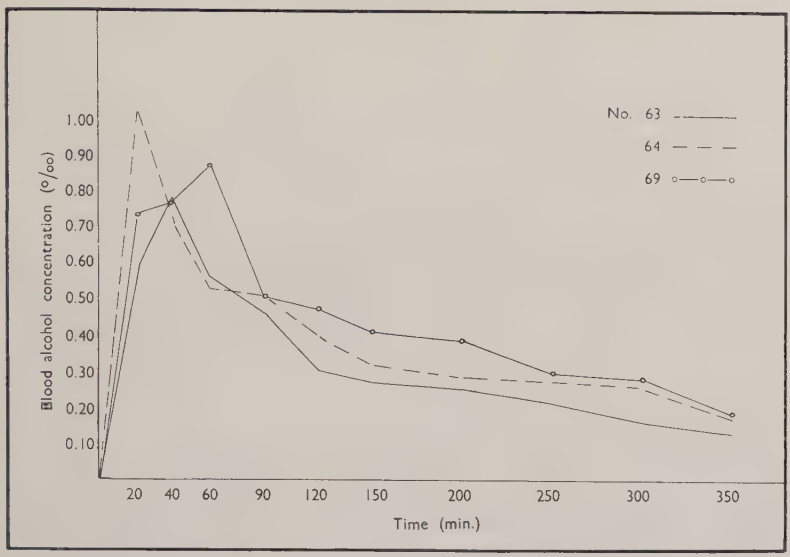

Fig. 8.— Blood alcohol curves of some patients suffering from hepatitis.

normal subjects. Its course in the postabsorptive phase is somewhat lower and more gently sloping than in normal subjects, and its final part stays above the curve of healthy subjects (Fig. 8 and 13). As the constants β and r are calculated by using only the blood alcohol concentration after an attained diffusion equilibrium, the shape of the curve is sufficient to indicate that the rate of the elimination of alcohol is retarded, and similarly, that r will be greater than normal. Thus, the average value of β *for men is* 0.00154 ± 0.00013, $\sigma = \pm 0.00037$ *and for women* 0.00176 ± 0.00008, $\sigma = \pm 0.00026$, *while the values of r are* 0.87 ± 0.027, $\sigma = \pm 0.076$ *and* $0.76 \pm 0{,}031$, $\sigma = \pm 0.103$, *respectively* (Table 37). The remarkably high value of r in the male patients makes one suspect that the alcohol was not completely absorbed, or that alcohol has escaped for some reason in the analysis, or it might still be figured that the diffusion of alcohol into the tissues is stimulated in jaundice. The first assumption is perhaps supported by the observation that in subjects No. 67, 70, 75, and 78 (Table 24), in whom a re-examination was made, the maximum alcohol concentration in blood was higher after recovery than in the experiment made during jaundice. Erwteman and Heeres (1938) have also observed a steep rise and a subsequent steep fall in the first phase of the blood alcohol curve of patients

TABLE 22

THE RESULTS OF THE CASES OF ACUTE HEPATITIS

a = first re-examination after treatment

b = second re-examination after treatment

No.	Date	Age	Stature cm	Body weight kg	Icterus index (Meulengracht)	Urine			β	r	b_{60}	$\frac{b_{60}}{p}$	T
						Iodine test	Ehrlich	Schlesinger					
Male													
63		44	179.0	68.5	1:90	+	+	−	0.0013	0.93	4.77	69.7	87.3
65	24. 4. −48	30	171.0	69.6	1:50	+	+	+	0.0019	0.82	6.47	92.9	89.5
65a	14. 5. −48	30	171.0	69.0	1:20	−	+	+	0.0020	0.76	6.33	91.7	83.9
69	1. 9. −48	51	168.0	73.8	1:140	+	+	−	0.0011	0.83	4.13	56.0	81.9
69a	1. 11. −48	51	168.0	71.0	1:13	−	−	−	0.0021	0.75	6.65	93.7	86.7
70	8. 9. −48	26	175.0	64.0	1:35	+	+	−	0.0014	0.98	5.41	84.5	89.8
70a	18. 5. −49	27	175.0	65.0	1:6	−	−	+	0.0019	0.81	6.05	93.0	82.7
73		30	169.0	68.0	1:15	+	−	+	0.0012	0.88	4.12	60.5	80.1
75	11. 10. −48	30	178.5	58.5	1:11	−	−	−	0.0017	0.92	5.49	93.8	81.4
75a	20. 7. −49	31	178.5	62.5	1:6	−	−	−	0.0020	0.75	5.76	91.7	75.6
76	12. 10. −48	20	177.5	66.0	1:40	+	−	−	0.0015	0.81	4.90	74.2	78.3
76a	27. 5. −49	21	177.5	66.0	1:5	−	−	−	0.0020	0.77	6.01	91.1	81.0
78	30. 12. −48	30	168.0	66.0	1:21	+	−	−	0.0022	0.75	6.43	97.7	81.3
78a	23. 5. −49	32	168.0	70.0	1:7	−	−	−	0.0020	0.63	5.41	77.3	71.3
Female													
64		22	159.0	51.0	1:110	+	+	+	0.0014	0.79	3.39	66.4	57.2
66	28. 4. −48	50	155.0	50.8	1:35				0.0018	0.77	4.19	82.6	60.0
66a	7. 5. −48	50	155.0	50.4	1:18				0.0018	0.75	4.21	83.5	59.0
66b	24. 2. −49	51	155.0	54.0	1:10				0.0017	0.85	4.62	85.6	69.0
67	13. 5. −48	43	165.5	80.3	1:120	+	−	−	0.0016	0.86	6.59	82.1	101.8
67a	13. 5. −49	44	165.5	72.0	1:5	−	−	−	0.0021	0.59	5.33	74.1	69.3
68		34	159.0	65.0	1:190	+	+	+	0.0016	0.67	4.20	64.6	64.3
71	9. 9. −48	28	160.0	49.0	1:28	+	−	+	0.0015	0.85	3.65	74.6	60.0
71a	19. 7. −49	29	160.0	49.0	1:15	+	+	−	0.0019	0.79	4.33	88.5	60.3
72		19	163.5	56.0	1:20	+	−	−	0.0017	0.67	3.84	68.5	56.5
74	8. 10. −48	41	154.5	65.2	1:37	+	−	−	0.0020	0.67	5.16	79.2	69.2
74a	9. 8. −49	42	154.5	66.0	1:7	−	−	−	0.0018	0.76	5.39	81.7	77.5
74b	27. 8. −49	42	154.5	64.8	1:7	−	−	−	0.0019	0.65	4.69	72.3	65.4
77		30	158.0	45.5	1:100	+	+	−	0.0022	0.74	4.43	97.5	55.8
79		18	154.0	50.0	1:35	+	+	+	0.0015	0.97	4.26	85.2	69.9
80		34	160.0	55.2	1:80	+	+	+	0.0021	0.64	4.48	81.2	57.6
81	18. 3. −49	47	162.0	56.6	1:80	+	+	+	0.0019	0.70	4.42	78.1	61.7
81a	6. 4. −49	47	162.0	56.0	1:25	−	−	+	0.0019	0.75	4.93	88.0	66.8
81b	28. 5. −49	47	162.0	60.0	1:9	−	−	−	0.0018	0.88	5.66	94.4	90.9

affected with acute hepatitis; however, as judged from the final part of the curve, the rate of the oxidation has been faster in their experiments than in mine. They administered 0.2 g of alcohol per kg body weight to their subjects. Staub and Peyser (1945) have observed a prolonged curve of alcoholaemia and a retarded fall to the original level in patients with lesions of the liver parenchyma. They have also observed a high maximum in these cases, even exceeding 1 $^{0}/_{00}$, whereas it remained in their normal group in general below 0.8 $^{0}/_{00}$. The experiments were made by using Widmark's micromethod, after administering 0.5 g of alcohol per kg body weight.

In eleven cases the alcohol experiment was repeated, when the icterus of the patient had considerably decreased or entirely disappeared, and in three cases the patients were re-examined twice; these patients were No. 66, 74, and 81 (Table 22 and 24). The weight of the subjects had remained practically unchanged. When the icterus had decreased or disappeared and the icterus index had returned towards normality, the value of β increased, except in the

TABLE 23

THE DISTRIBUTION OF THE CONSTANTS β AND r IN THE GROUP OF ACUTE HEPATITIS, ARRANGED ACCORDING TO THEIR NUMERICAL VALUE

β	Males	Females
$<$ 0.0012	1	0
0.0012—0.0014	3	1
0.0015—0.0017	2	5
0.0018—0.0020	1	3
0.0021—0.0023	1	2
$>$ 0.0023	0	0
Total	8	11
r		
0.50—0.55	0	0
0.56—0.60	0	0
0.61—0.65	0	1
0.66—0.70	0	4
0.71—0.75	1	1
0.76—0.80	0	2
0.81—0.85	3	1
0.86—0.90	1	1
$>$ 0.90	3	1
Total	8	11

TABLE 24

THE BLOOD ALCOHOL CONCENTRATION (‰) IN THE CASES OF ACUTE HEPATITIS

a = first re-examination after treatment
b = second re-examination after treatment

No.	Sex	Time									
		20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
63	Male	0.54	0.79	0.55	0.47	0.31	0.28	0.27	0.23	0.17	0.14
64	Female	1.05	0.71	0.54	0.52	0.31	0.33	0.29	0.28	0.27	0.18
65	Male	0.63	0.61	0.49	0.43	0.36	0.27	0.22	0.13	0.03	0.00
65a	»	0.69	0.66	0.55	0.48	0.36	0.32	0.25	0.12	0.07	0.00
66	Female	1.01	0.71	0.54	0.47	0.34	0.33	0.27	0.18	0.17	0.05
66a	»	0.81	0.70	0.58	0.43	0.39	0.37	0.27	0.19	0.09	0.08
66b	»	0.43	0.66	0.58	0.42	0.33	0.26	0.25	0.13	0.11	0.02
67	»	0.69	0.66	0.53	0.39	0.37	0.24	0.18	0.14	0.14	0.12
67a	»	0.38	0.50	0.79	0.64	0.60	0.58	0.42	0.27	0.23	0.14
68	»	0.36	0.79	0.72	0.62	0.53	0.44	0.40	0.34	0.31	0.19
69	Male	0.73	0.76	0.87	0.50	0.48	0.41	0.40	0.30	0.30	0.19
69a	»	0.93	0.66	0.53	0.48	0.39	0.33	0.19	0.13	0.04	0.00
70	»	0.26	0.54	0.45	0.45	0.31	0.28	0.18	0.09	0.08	0.07
70a	»	0.75	0.58	0.46	0.45	0.43	0.38	0.14	0.08	0.06	0.00
71	Female	0.40	0.56	0.50	0.46	0.41	0.36	0.31	0.22	0.12	0.10
71a	»	0.27	0.50	0.62	0.54	0.36	0.36	0.28	0.13	0.03	0.03
72	»	0.88	0.71	0.65	0.55	0.55	0.48	0.45	0.33	0.19	0.18
73	Male	0.28	0.49	0.63	0.46	0.47	0.40	0.29	0.28	0.26	0.16
74	Female	0.60	0.97	0.70	0.58	0.43	0.41	0.38	0.26	0.21	0.03
74a	»	0.45	0.74	0.66	0.55	0.46	0.34	0.25	0.18	0.17	0.04
74b	»	0.39	0.63	0.77	0.57	0.52	0.52	0.48	0.33	0.14	0.13
75	Male	0.58	0.62	0.50	0.44	0.32	0.27	0.10	0.06	0.03	0.04
75a	»	0.86	0.61	0.66	0.56	0.45	0.25	0.22	0.14	0.04	0.01
76	»	0.66	0.58	0.51	0.49	0.46	0.35	0.26	0.23	0.20	0.08
76a	»	0.58	0.62	0.55	0.53	0.35	0.34	0.25	0.15	0.04	0.00
77	Female	0.77	0.69	0.58	0.44	0.41	0.28	0.14	0.09	0.03	0.00
78	Male	0.44	0.52	0.61	0.60	0.38	0.32	0.16	0.03	0.03	0.00
78a	»	0.96	1.02	0.72	0.69	0.50	0.40	0.32	0.30	0.19	0.12
79	Female	0.46	0.54	0.70	0.44	0.30	0.26	0.22	0.16	0.08	0.00
80	»	0.89	0.77	0.69	0.63	0.49	0.39	0.33	0.25	0.16	0.08
81	»	0.54	0.66	0.72	0.58	0.49	0.41	0.34	0.24	0.13	0.09
81a	»	0.45	0.67	0.68	0.57	0.42	0.32	0.24	0.15	0.07	0.04
81b	»	0.33	0.70	0.48	0.43	0.37	0.27	0.19	0.06	0.01	0.01

male patient No. 78 and in the female patients No. 66, 74, and 81. The terminal course of the curve now showed a steeper fall, and the oxidation of alcohol seemed to be improved. Similarly, the value of *r* is distinctly reduced in the male subjects, and also in the female subjects at the second examination, but it rose again in the third experiment. The last value has been calculated only from three cases, and thus no conclusions can be made in respect of so few

cases. Table 23 shows β and r as arranged according to their numerical values.

b_{60} *was* 5.22 $g \pm$ 0,32, *with* $\sigma = \pm$ 0,91 *in the male cases of hepatitis, and* 4.42 $g \pm$ 0,42, *with* $\sigma = \pm$ 0,86 *in the female ones.* The values are smaller than those observed in the group of healthy subjects.

The ability to metabolize alcohol, as expressed per kg body weight and per hour, was 78.6 *mg* $\pm$ 5.6, *with* $\sigma = \pm$ 15.8 *in men, and* 78.2 *mg* $\pm$ 2.9, *with* $\sigma = \pm$ 9.5 *in women.* Both b_{60} and b_{60}/p increase with the disappearance of the jaundice, and the ability to metabolize alcohol seems to improve, as is observable in Table 22.

The value of *T among the male jaundice patients* was slightly higher than the respective value in the normal group; this evidently depends on the rather high value of r in this group, since the body weight was the same in both groups. The mean value of T was 83.6 $g \pm$ 1.6, *with* $\sigma = \pm$ 4.5. *The value of T among the female* patients was almost the same as in healthy women, i.e. 64.9 $g \pm$ 4.0, *with* $\sigma = \pm$ 13.2.

Serianni and Lolli (1938) have made blood alcohol studies on fasting healthy subjects and on patients suffering from liver diseases, by administering 0.5 ml of 20 per cent alcohol per kg body weight per os. Their material comprises cases of liver cirrhosis, cholecystitis and cohlelithiasis, accompanied by jaundice. According to them, there is no difference observable between the alcohol curves of these patients and healthy subjects. However, if alcohol is given to healthy subjects some time after a mixed meal, a much lower alcohol curve is obtained than in fasting subjects, as generally observed, but in liver diseases, the blood alcohol curve after a meal remains at the same level as in the same subjects fasting before the ingestion of alcohol. Serianni and Lolli (1938) ascribe this to a stimulating effect of food on the metabolism of the healthy liver, which effect enhances the oxidation of alcohol. This is possible only in a healthy liver. Erwteman and Heeres (1938)have obtained differing curves in cases of hepatitis, liver cirrhosis and liver tumours. According to them an alcohol tolerance test has significance in the differential diagnosis. It was already mentioned that their cases of acute hepatitis showed a high and short blood alcohol curve. It is high also in liver cirrhosis, but the terminal part of the curve is rising, and in patients with liver tumours, they again observed a plateau in some of the cases, or a slow, gently sloping fall in others.

TABLE 25

THE RESULTS OF THE CASES OF LIVER CIRRHOSIS

A case of carcinoma of liver in brackets

No.	Sex	Age	Stature cm	Body weight kg	Icterus index (Meulengracht)	Urine			β	r	b_{60}	$\frac{b_{60}}{p}$	T
						Iodine test	Ehrlich	Schlesinger					
82	M	33	184	79.0	1:8	—	—	+	0.0017	0.70	5.64	71.3	83.5
83	„	39	172	74.2	1:6	—	—	—	0.0019	0.68	5.74	77.3	79.2
84	„	29	162	54.4	1:11	—	+	+	0.0015	0.77	3.78	69.5	61.0
85	„	37	181	75.0	1:5	—	—	—	0.0019	0.71	6.14	81.9	84.0
86	F	65	?	33.0	1:20	—	+	+	0.0016	0.83	2.62	79.5	40.6
(87	„	54	156	35.2	1:50	+	—	+	0.0017	0.84	2.92	83.1	44.1)

LIVER CIRRHOSIS

There was an opportunity to include five cases of liver cirrhosis to this section of the writer's material (Table 25 and 26, Fig. 9). Case No. 82 had syphilitic liver cirrhosis, No. 83, 84, and 85 had a record of long lasting use of alcohol, and No. 86 was a case of biliary cirrhosis due to an obstructing gall stone. The latter was the only patient with jaundice in this group. He had already been icteric for a period of two years, but, for some reason or other, had not been operated upon in due time.

The blood alcohol curves of the liver cirrhosis cases of the present work are very similar to those of the hepatitis patients. The first part resembles the corresponding part in the normal curves also in this group (Fig. 4), and the terminal part is extended and the disappearance of alcohol retarded (No. 82, 84, and 86). *The mean value of the* β *of the male patients is* 0.00175 ± 0.00010, *with* $\sigma = \pm 0.00019$, and *that of* r 0.715 ± 0.019, *with* $\sigma = \pm 0.039$.

It is questionable whether an ample and continuous consumption of alcohol plays a rôle in the genesis of liver cirrhosis. (Widmark 1931, Josephson and Asplund 1948). Widmark (1931), for instance, was not able to observe any hepatic lesion in dogs given alcohol per os

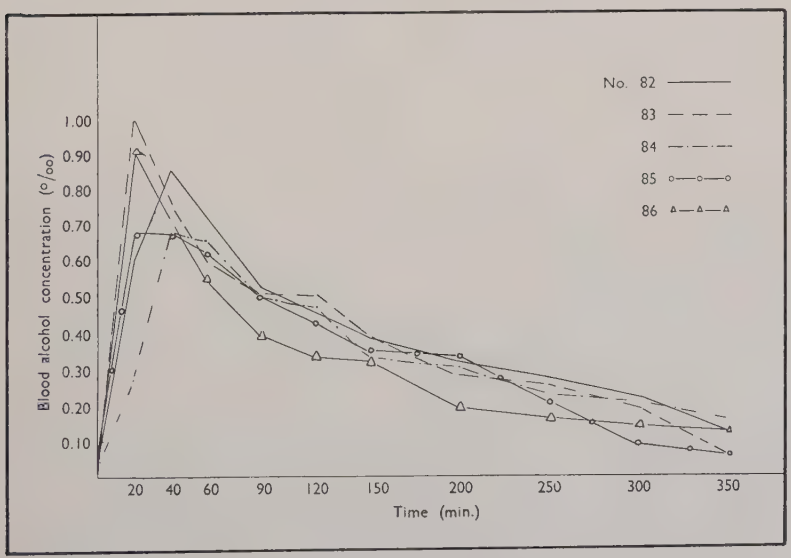

Fig. 9.— The blood alcohol curves of the patients affected with liver cirrhosis.

TABLE 26

THE BLOOD ALCOHOL CONCENTRATION (‰) IN THE CASES OF LIVER CIRRHOSIS

A case of carcinoma of liver in brackets

No.	Sex	Time									
		20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
82	Male	0.58	0.86	0.72	0.53	0.48	0.39	0.33	0.29	0.24	0.14
83	»	0.90	0.76	0.61	0.51	0.52	0.39	0.30	0.28	0.21	0.09
84	»	0.27	0.69	0.65	0.60	0.47	0.33	0.31	0.23	0.23	0.17
85	»	0.68	0.67	0.62	0.51	0.43	0.36	0.34	0.23	0.10	0.07
86	Female	0.91	0.71	0.55	0.39	0.34	0.33	0.20	0.17	0.16	0.15
(87	»	0.69	0.74	0.63	0.49	0.45	0.36	0.30	0.24	0.19	0.11)

daily during several years. According to Jellinek (1942) the opinion, that the poor and unbalanced nutrition, avitaminosis and digestive disturbances are the cause of liver cirrhosis seems to be quite general. Halonen and Saksela (1946) assume that an ample consumption of alcohol in all probability increases the frequency of cirrhosis, but according to them, this is a subject difficult to decide upon. Abderhalden and Wertheimer (1927) have studied the rôle of sex in mice, in connection with prolonged use of alcohol; they observed that when 50 male and 50 female mice were daily given from 0.1 to 0.2 ml of 30 per cent aethyl alcohol subcutaneously, the female mice proved more resistant to the toxic effects of alcohol, for 42 of the male animals — but only 15 of the female ones — died within a fortnight.

It is difficult to judge to what extent the liver cirrhosis observed in the cases No. 83, 84, and 85, which had a record of ample consumption of alcohol, had exerted a decreasing influence on the constant β. Starting from the assumption that the liberal use of alcohol stimulates its elimination and thus increases the value of β, it may be figured that if these subjects had not consumed much alcohol, their values of β would have been smaller still, due to cirrhosis.

Case No. 87 was a liver carcinoma. It does not differ markedly from the cases of liver cirrhosis, either in respect of the blood alcohol concentration or as to the value of the constants. This single case does not, of course, permit of any conclusions.

The present study, therefore, does not support the view of Erwteman and Heeres (1938), according to which the blood alcohol curves

of the various diseases of the liver are so different that an alcohol tolerance test has significance in the differential diagnosis. On the other hand, such a test which is cumbersome in practice and perhaps not quite harmless has no use, especially as there are several reliable and more easily-made tests of the liver function. The blood alcohol curves of Staub and Peyser (1945) and those obtained in the present work on patients affected with parenchymatous lesions of the liver, are similar.

HYPERTHYREOSIS

The syndrome of hyperthyreosis is characterized by an acceleration of the basal metabolism of the body. A patient suffering from this disease is restless, anxious, easily startled, perspires and trembles easily, experiences palpitation and loses weight. Moreover, the intestinal motility may be increased during this disease. Often one is able to palpate an enlarged or nodous thyroid. When these symptoms are present, the diagnosis of hyperthyreosis may be made with fair certainty. The determination of the basal metabolism was included in the methods of examination, but as its reliability may be questionable, a diagnosis was not made solely relying upon it, but great importance has been given to the clinical symptoms. A determination of the blood galactose concentration after an administration of galactose has also been made on the patients.

Dell'Acqua (1932) has studied the shape of the blood alcohol curve in hyperthyreotic patients, admittedly on a very small material, consisting of 4 cases. He gave 0.25 g of alcohol per kg body weight in 100 ml of water, and observed the course of the blood alcohol level at 30, 90, and 180 min. after the administration of the alcohol. The curves he obtained on the hyperthyreotic patients are slightly lower and flatter than those of his normal subjects. Erwteman and Heeres (1938) have arrived in their studies at a result similar to that of Dell'Acqua (1932). Erwteman and Heeres (1938) obtained higher curves in these cases after drugs improving the circulation. Widmark (1935) has given from 10 to 36 mg of thyroxin to dogs, without observing any affect on the rate of the elimination of alcohol. However, by using dinitrophenol he effected an intense stimulation of the elimination of alcohol. He assumes that this depends either on an increased vaporisation of alcohol because of increased ventilation or on an increased use of fuel, due to the high basal metabolism.

TABLE 27

THE RESULTS OF THE CASES OF HYPERTHYREOSIS

a = re-examination after treatment

No.	Date	Age	Stature cm	Body weight kg	Basal metabolism %	β	r	b_{60}	$\frac{b_{60}}{p}$	T
					Male					
94		23	173.5	68.0	+ 25	0.0026	0.51	5.39	79.2	61.7
98		41	168.5	72.0	+ 37	0.0024	0.77	8.07	112.1	95.7
103		25	170.0	60.0	+ 31	0.0025	0.55	4.85	80.9	57.2
					Female					
89	7.4—48	58	159.0	60.6	+ 33	0.0022	0.66	5.16	85.1	65.6
89 a	12.5—48	58	159.0	62.5	+ 11	0.0020	0.65	4.86	77.7	65.0
90	8.4—48	63	157.0	62.3	+ 68	0.0032	0.53	6.37	102.2	64.7
90 a	8.9—49	64	157.0	73.0	+ 29	0.0021	0.68	6.38	87.4	81.7
91		46	162.0	42.4	+ 48	0.0018	0.76	3.55	83.7	49.9
92		34	155.0	45.0	+ 42	0.0021	0.89	5.01	111.2	65.3
93	3.9—48	25	162.0	54.0	+ 15	0.0014	0.80	3.62	67.0	61.1
93 a	6.5—49	26	162.0	56.0	+ 5	0.0021	0.63	4.46	79.7	57.5
95	17.9—48	35	162.0	48.0	+ 6	0.0016	0.95	4.30	89.5	67.0
95 a	26.10—49	36	162.0	50.0	+ 3	0.0020	0.73	4.44	88.8	58.5
96		73	163.0	57.0	+ 63	0.0017	0.80	4.71	82.7	69.0
97		56	151.5	35.0	+ 22	0.0017	0.83	2.97	84.8	44.0
99		55	149.0	63.0	+ 47	0.0025	0.63	6.00	95.2	69.9
100		37	168.0	56.0	+ 30	0.0022	0.66	4.96	88.5	61.6
101		54	162.0	54.0	+ 36	0.0029	0.55	5.13	95.0	55.4
102		36	162.5	63.0	+114	0.0029	0.50	5.42	86.1	58.5

The writer's material comprises 3 male and 12 female patients (Table 27). The mean body weight of the former was 66.5 kg, and that of the latter was a little lower than the average weight of the healthy control group, 53.4 kg. The blood alcohol curves of the hyperthyreosis cases were in general slightly lower than normal, except for the male patients No. 94 and 103 and the female cases No. 101 and 102. The terminal part of the curve falls at approximately the same rate as in healthy subjects, and certainly not more slowly. There is no typical hyperthyreosis curve worth presenting, but the blood alcohol concentrations are shown in each case separately in Table 29.

Among the men, cases No. 94 and 103 had previously used rather great amounts of alcohol. All the other subjects had been almost total abstainers. This fact renders it more difficult to draw conclusions particularly as regards the rate of the elimination of alcohol and

TABLE 28

THE DISTRIBUTION OF THE CONSTANTS β AND r IN THE HYPERTHYREOSIS GROUP, ARRANGED ACCORDING TO NUMERICAL VALUE

β	Males	Females
0.0014—0.0020	0	5
0.0021—0.0025	2	4
0.0026—0.0030	1	2
> 0.0030	0	1
Total	3	12
r		
< 0.50	0	0
0.50—0.55	2	3
0.56—0.60	0	1
0.61—0.65	0	0
0.66—0.70	0	2
0.71—0.75	0	0
0.76—0.80	1	3
0.81—0.85	0	1
0.86—0.90	0	1
> 0.90	0	1
Total	3	12

TABLE 29

THE BLOOD ALCOHOL CONCENTRATION ($^0/_{00}$) IN THE CASES OF HYPERTHYREOSIS

a = re-examination after treatment

No.	Sex	Time									
		20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
89	Female	0.25	0.52	0.59	0.57	0.49	0.44	0.35	0.24	0.10	0.00
89a	»	0.37	0.53	0.58	0.73	0.55	0.46	0.35	0.30	0.15	0.08
90	»	0.53	0.61	0.52	0.47	0.39	0.25	0.19	0.11	0.00	0.00
90a	»	0.25	0.27	0.58	0.70	0.53	0.39	0.26	0.19	0.11	0.00
91	»	0.45	0.75	0.65	0.55	0.34	0.29	0.25	0.22	0.14	0.04
92	»	0.53	0.49	0.46	0.41	0.28	0.21	0.07	0.04	0.00	0.00
93	»	0.61	0.69	0.57	0.56	0.42	0.36	0.32	0.31	0.20	0.16
93a	»	0.81	1.05	0.68	0.61	0.55	0.45	0.38	0.28	0.13	0.08
94	Male	0.54	1.11	1.14	0.81	0.73	0.50	0.40	0.27	0.24	0.12
95	Female	0.53	0.68	0.57	0.46	0.32	0.28	0.14	0.04	0.03	0.00
95a	»	0.57	0.97	0.63	0.53	0.39	0.32	0.31	0.15	0.05	0.03
96	»	0.71	0.74	0.62	0.47	0.40	0.31	0.22	0.14	0.14	0.09
97	»	0.36	0.45	0.56	0.45	0.37	0.35	0.24	0.16	0.12	0.00
98	Male	0.27	0.58	0.49	0.41	0.28	0.27	0.10	0.06	0.00	0.00
99	Female	0.63	0.93	0.80	0.51	0.49	0.34	0.22	0.10	0.02	0.01
100	»	0.43	0.75	0.73	0.54	0.47	0.41	0.24	0.15	0.09	0.06
101	»	0.57	0.77	0.79	0.64	0.55	0.42	0.32	0.16	0.04	0.00
102	»	0.67	0.99	0.93	0.73	0.67	0.48	0.35	0.32	0.19	0.00
103	Male	0.34	0.57	1.03	0.70	0.63	0.58	0.39	0.30	0.12	0.12

possibly also in respect of the value of r. The value of β *for the men was* 0.00250 $\pm$ 0.00006, *with* $\sigma = \pm$ 0.00010, *and for the women* 0.00218 $\pm$0.00015, *with* $\sigma = \pm$ 0.00051. To what extent a liberal use of alcohol by the men had affected the value of β is again difficult to judge; the value of β for women was about the same as in the normal group. On the other hand, it was just among the hyperthyreotic women out of the whole material that the highest values of β occurred (Table 27: No. 90, 99, 101, and 102).

The value of r of the male patients is rather low, 0.610, $\pm$0.081, *with* $\sigma = \pm$0.140 but the number of cases is too low to allow of definite conclusions. *In women r was* 0.713 $\pm$0.042, *with* $\sigma = \pm$0.140, which is slightly higher than normal.

Four of the women were examined again after treatment. The cases No. 89, 90, and 95 were treated with methylthiouracil, and case No. 93 had been subjected to strumectomy. In all these cases the blood alcohol curve ran parallel to the first curve, slightly above it.

b_{60} *is in the group of hyperthyreotic males* 6.10 *g* $\pm$ 0.99, *with* $\sigma = \pm$ $\pm$ 1.41, which is slightly higher than the corresponding value of healthy subjects, but it may not be justified, on account of so few cases, to draw the conclusion, that the ability to metabolize alcohol is higher in hyperthyreotic patients than in healthy subjects. *In the women,* who formed the majority in this group, it is on the contrary smaller than normal, i.e. 4.77 *g* $\pm$ 0.29, *with* $\sigma = \pm$ 1.01.

The value of b_{60}/p in the hyperthyreosis group, both in men and in women, is slightly higher than normal: *in males* it was 90.7 *mg* $\pm$ 10.7, *with* $\sigma = \pm$ 18.5, and *in females* 89.3 *mg* $\pm$ 3.2, *with* $\sigma = \pm$ 11.0.

The results of the re-examinations are too few to make any definite conclusions possible, for some cases show a slight increase and others a decrease after the treatment.

The value of T both *in men* and *women* is a little below the normal values; in the former it was 71.5 *g* $\pm$ 12.1, *with* $\sigma = \pm$ 21.0, *and in the latter* 61.0 *g* $\pm$ 2.8, *with* $\sigma = \pm$ 7.9.

DIABETES MELLITUS

The material consists of 21 subjects suffering from diabetes; 13 of these were men and 8 women. The mean body weight of the former was 63.6 kg, and of the women 59.6 kg. The subjects belonging

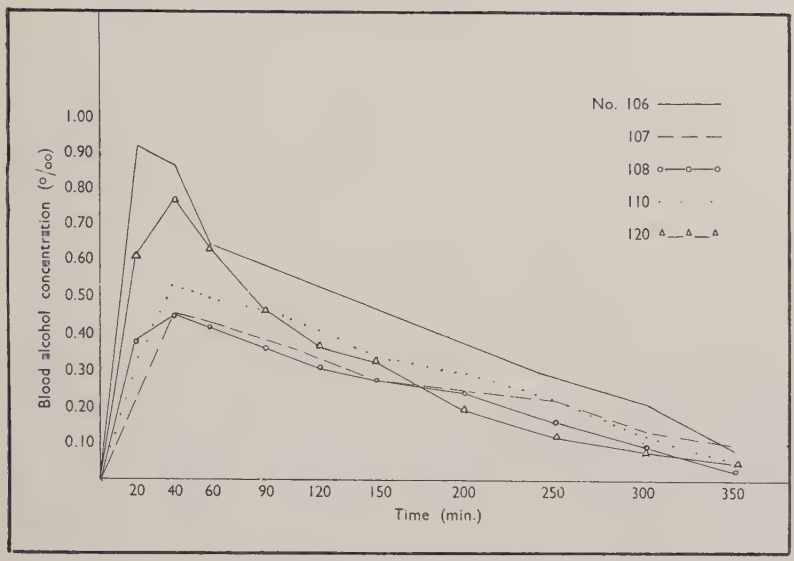

Fig. 10.— Blood alcohol curves of some of the diabetic patients.

to this group were in general quite unused to alcohol; a minority of them had used it in very small amounts.

The blood alcohol concentration after an ingestion of alcohol was in most cases lower than in normal subjects (Table 32). In general the curves are low and flat. There are, however, also such cases as No. 104, 106, 114, 116, 118, and 122, where the maximum concentration of blood alcohol is high and the time needed for attaining it short. In these cases too, the curve falls rapidly, and its latter part is fairly low (Fig. 10). Dell'Acqua (1932) and Erwteman and Heeres (1938) have, on the contrary, obtained high curves by using Widmark's micromethod, and the highest were those made after a fast of a few days or in precoma. From this they draw the conclusion that in these cases the lack of glycogen in the liver is responsible for this shape of the curve. To what extent volatile substances, oxidizable with dichromate and thus disturbing the alcohol analyses, have possibly been present in blood in the above conditions, is not evident. In addition, Dell'Acqua (1932) has studied the effect of exercise on the level of blood alcohol, and has noticed that the curve of a diabetic patient then remains clearly below the resting curve. Furthermore, he obtained a lower curve after an injection of adrenaline than without this substance in one

diabetic patient. It is known that adrenaline converts glycogen to sugar and thus reduces the already low store of liver glycogen, which may explain this phenomenon. Gremels (1948) in his studies on metabolism has observed that alcohol taken together with sucrose or pure laevulose increases the blood alcohol and sugar levels but very little, from which he draws the conclusion that alcohol is burned rapidly in the presence of sugar. On the other hand, it has been investigated and observed that the absorption of alcohol with food is slower, and thus the level of blood alcohol remains lower.

The terminal part of the curves of the diabetes group in the present work is about similar to that in the normal material. Admittedly, there were also subjects with a very slow elimination of alcohol (Table 30 and 31). The value of the β *of men was* 0.00180 ± 0.00017, *with* $\sigma = \pm 0.00060$, *and that of r was* 0.806 ± 0.047, *with* $\sigma = 0.169$. The cases No. 107, 108, and 124 were young and took alcohol for

TABLE 30

THE DISTRIBUTION OF THE CONSTANTS β AND r IN THE DIABETES MELLITUS GROUP, ARRANGED ACCORDING TO NUMERICAL VALUE

β	Males	Females
<0.0012	1	0
0.0012—0.0014	3	2
0.0015—0.0017	3	3
0.0018—0.0020	3	0
0.0021—0.0023	2	1
0.0024—0.0026	0	1
0,0027—0.0029	0	1
0,0030—0.0032	0	0
>0.0032	1	0
Total	13	8
r		
0.50—0.55	1	0
0.56—0.60	0	1
0.61—0.65	1	0
0.66—0.70	0	1
0.71—0.75	4	1
0.76—0.80	2	0
0.81—0.85	1	1
0.86—0.90	0	3
0.91—0.95	1	0
>0.95	3	1
Total	13	8

TABLE 31

THE RESULTS OF THE CASES OF DIABETES MELLITUS

No.	Age	Stature cm	Body weight kg	β	r	b_{60}	$\frac{b_{60}}{p}$	T
				Male				
104	68	162.0	68.4	0.0016	0.84	5.51	80.6	84.9
105	23	172.0	71.0	0.0015	0.76	4.92	69.3	78.2
106	50	172.5	77.5	0.0021	0.61	6.04	77.9	77.4
107	15	160.5	44.0	0.0011	1.03	3.14	71.3	61.2
108	17	164.0	50.0	0.0013	1.05	4.12	82.5	72.9
109	67	175.0	62.0	0.0019	0.73	5.21	84.1	71.3
113	69	168.0	60.5	0.0034	0.51	6.18	102.1	61.5
115	18	?	70.2	0.0017	0.72	5.30	75.6	77.2
117	42	166.0	72.0	0.0020	0.75	6.56	91.1	86.8
120	44	175.0	55.0	0.0026	0.77	4.98	90.5	67.2
122	39	181.5	72.0	0.0022	0.72	6.68	92.8	85.0
123	32	156.0	58.0	0.0014	0.93	4.67	80.5	77.2
124	21	181.0	67.0	00.012	1.06	5.08	75.9	96.8
				Female				
110	23	167.5	60.0	0.0016	0.84	4.69	78.2	73.6
111	59	160.0	56.0	0.0016	0.86	4.56	81.5	71.1
112	54	153.5	56.0	0.0013	0.96	4.04	72.1	74.0
114	51	158.5	60.0	0.0028	0.57	5.73	95.6	63.1
116	62	153.0	59.5	0.0024	0.66	5.77	97.0	68.3
118	21	149.0	65.0	0.0022	0.73	6.32	97.3	79.3
119	52	172.0	67.1	0.0014	0.90	5.10	76.0	86.0
121	41	157.5	53.4	0.0017	0.89	4.87	91.1	71.8

the first time at this experiment. It is just these who show markedly low values of β and, correspondingly, very high values of r. The curves are in these cases rather low and flat. These curves were the only ones in the present material (142 alcohol tolerance tests) with a value of r exceeding unity. Schmidt (1935) observed a value of r exceeding unity in 6 of 66 alcohol tolerance tests on normal subjects, with a maximum at 1.15; in 12 experiments r exceeded 0.95.

The value of the β *of female subjects was* 0.00188 ± 0.00019, *with* $\sigma = \pm 0.00053$, *and the value of r was* 0.80 ± 0.047, *with* $\sigma = \pm 0.126$. There were also among them two, No. 112 and 119, with a very small value of β, but correspondingly also subjects with a β above normal. The distribution of the numerical values of β is shown in Table 30.

The observation that β in the group of diabetic patients was on an average smaller than in healthy subjects, does not, to the writer's

TABLE 32

THE BLOOD ALCOHOL CONCENTRATION (‰) IN THE CASES OF DIABETES MELLITUS

No.	Sex	Time									
		20′	40′	60′	90′	120′	150′	200′	250′	300′	350′
104	Male	0.82	0.56	0.49	0.45	0.39	0.33	0.27	0.24	0.15	0.00
105	»	0.68	0.70	0.57	0.53	0.45	0.42	0.41	0.25	0.21	0.12
106	»	0.91	0.86	0.64	0.59	0.53	0.48	0.38	0.28	0.22	0.09
107	»	0.23	0.45	0.43	0.39	0.34	0.27	0.24	0.22	0.12	0.09
108	»	0.36	0.45	0.41	0.36	0.30	0.27	0.24	0.15	0.09	0.01
109	»	0.40	0.70	0.65	0.55	0.42	0.31	0.26	0.19	0.14	0.05
110	Female	0.30	0.54	0.50	0.47	0.42	0.34	0.30	0.23	0.12	0.05
111	»	0.36	0.50	0.45	0.44	0.43	0.32	0.31	0.19	0.06	0.04
112	»	0.36	0.51	0.43	0.43	0.36	0.34	0.26	0.23	0.14	0.08
113	Male	0.47	0.59	0.64	0.51	0.35	0.27	0.14	0.06	0.00	0.00
114	Female	0.96	0.96	0.66	0.55	0.55	0.35	0.26	0.17	0.02	0.00
115	Male	0.25	0.35	0.45	0.51	0.47	0.43	0.36	0.26	0.16	0.08
116	Female	0.90	0.93	0.74	0.67	0.38	0.24	0.14	0.08	0.04	0.04
117	Male	0.38	0.66	0.63	0.48	0.40	0.32	0.23	0.13	0.04	0.04
118	Female	0.46	0.98	0.66	0.54	0.39	0.27	0.10	0.06	0.06	0.01
119	»	0.34	0.53	0.50	0.46	0.12	0.36	0.27	0.18	0.09	0.04
120	Male	0.61	0.77	0.64	0.47	0.37	0.33	0.18	0.11	0.07	0.04
121	Female	0.49	0.53	0.50	0.48	0.32	0.25	0.17	0.11	0.06	0.02
122	Male	0.73	1.01	0.67	0.49	0.37	0.35	0.26	0.18	0.00	0.00
123	»	0.64	0.52	0.42	0.40	0.37	0.31	0.25	0.18	0.08	0.06
124	»	0.50	0.44	0.38	0.34	0.32	0.31	0.26	0.15	0.11	0.06

judgement, justify the conclusion that the elimination of alcohol is slower than normal in diabetes, for such a difference may be within the range of individual variability. Moreover, the dispersion of β was very great in this group. (See: statistical treatment.)

Koehler *et al.* (1944), studying the alcohol metabolism of diabetic patients, has arrived at the conclusion that the elimination of alcohol in diabetic patients is similar to that in healthy subjects.

No definite relation was observed in the present work between the blood sugar level, eventual ketonuria, and the constants β and r. Evidently, the blood level of ketone bodies has been too low significantly to affect the results of the analyses even in those cases where Gerhard's and Legal's tests on urine were positive, since the blood alcohol concentration remains lower in the diabetes group than in the healthy subjects.

It is difficult to assess why the value of r is so high in the cases No. 107, 108, 112, 119, and 124. All were hospital patients, and thus the diet has been under strict control; therefore a retardation of the absorption of alcohol because of food at least ought to be excluded.

It is known that diabetic patients may often exhibit symptoms of gastritis, but there are investigations which show that the absorption of alcohol from an inflamed — and hyperaemic — stomach is, on the contrary, even more rapid than normal. That the diffusion of alcohol from blood to the tissues would be accelerated in these cases because of the simultaneous absorption, for some reason, and thus would reduce the alcohol concentrations observed in the blood analyses, is a hypothesis remaining without proof.

b_{60} *was* 5.26 *g* $\pm$ 0.27, *with* $\sigma = 0.98$ *for the men of the diabetes group, and* 5.14 *g* $\pm$ 0.26, *with* $\sigma = \pm 0.75$, *for the women.*

b_{60}/p *was respectively* 82.6 *mg* $\pm$ 2.6, *with* $\sigma = \pm 9.4$ *for the men, and* 86.1 *mg* $\pm$ 3.6, *with* $\sigma = \pm 10.3$, *for the women.* According to this, the ability to metabolize alcohol seems to be almost the same in diabetic patients and healthy subjects.

The value of the T of men is of the same order as that in health, that of women slightly higher (Table 37). However, the body weight and the value of r which affect T are both higher in the group of diabetic women than among normal subjects.

During an alcohol tolerance test the blood sugar level seems to fall in almost all cases of diabetes in the present material, in conformity with the results of previous studies (Allen and Wishart 1922, Fuller 1922, Hunt 1930, and Edkins and Murray 1931).

X

STATISTICAL TREATMENT OF THE RESULTS

THE EFFECT OF THE METHODICAL ERROR ON THE FACTORS CHARACTERIZING THE INDIVIDUAL ALCOHOL METABOLISM

For assessing the accuracy of the method, it was assumed — as is usual and in several ways proved by experience — that the result of an individual measurement is a random variable which is, at least approximately, normally distributed (Cramér 1949). In the investigation, the determination of each blood alcohol concentration was made in duplicate (in some cases in triplicate), and the mean value of these was taken as a basis for the calculations. The standard error of this mean, which gives a measure of the accuracy of the method, may be expected to remain unchanged in the individual cases, as the determination was always carried out by using the same method. An estimate for it is obtained by choosing k cases at random, and by calculating the following formula for them (Cramér 1949):

$$d(\bar{x}_v) = \pm \frac{1}{2} \sqrt{\frac{1}{k} \sum_{v=1}^{k} (x_{v1} - x_{v2})^2}$$

where x_{v1} and x_{v2} denote the two values of a duplicate determination. The higher the number k, the more appropriate this estimate is to be used in the sense of an ordinary »standard error». In the present work, this calculation was made by selecting 120 duplicate determinations at random, and the result was:

the standard error of the blood alcohol determination d (x) = 0.0109 ‰.

The factors β and c_0 are both linear functions from certain values of x_v. Since each x_v is a random variable with normal distribution, β and c_0 are also random variables with a normal dis-

tribution. For their standard error, the following formula is derived (Cramér 1949):

$$d(\beta) = \pm d(x) \frac{\sqrt{n}}{\sqrt{n \sum t_v^2 - (\sum t_v)^2}}$$

$$d(c_0) = \pm d(x) \frac{\sqrt{\sum t_v^2}}{\sqrt{n \sum t_v^2 - (\sum t_v)^2}}$$

As mentioned above, the values of t_v used for the calculation of β and c_0 are not the same all over the material, but there are different possibilities. Table 33 shows these possibilities (t_f is first, t_l the last of the relevant values of t), the corresponding factors n, $d(\beta)$, and $d(c_0)$, and the last column shows the distribution of the material as a whole among the different classes.

Because the factor c_0 is in the denominator of the formulas of r, b_{60}, b_{60}/p, and of T, these factors are random variables with a distribution differing from normal. Therefore, one may not apply the concept of standard error as such, as it presumes the normal distribution of the variable. However, a view of the accuracy of r may be obtained by examining the limits:

$$\frac{A}{[c_0 + d(c_0)]\,p}, \text{ and } \frac{A}{[c_0 - d(c_0)]\,p}$$

The value of r belongs within these limits with the same probability as a normally distributed variable within the limits of its standard error.

TABLE 33

STANDARD ERRORS OF β AND c_0

From t_f to t_l	n	d (β)	d (c_0)	m
40—350	9	0.000035	0.0071	32
40—300	8	0.000045	0.0078	1
60—350	8	0.000040	0.0085	53
60—300	7	0.000051	0.0095	3
90—350	7	0.000046	0.0105	28
90—300	6	0.000061	0.0121	1
120—350	6	0.000055	0.0106	4
120—300	5	0.000075	0.0160	1
				123

The problem is more complicated as to the constants b_{60}, b_{60}/p, and T, because the formulas of these factors contain the quotient of two mutually dependent random variables, β and c_0. However, by making use of an auxiliary factor $\gamma = \sum t_v x_v$, which is normally distributed $[d(\gamma) = \pm d(x) \mid \sum t_v^2]$, and independent of c_0, it is possible to break down the formula of, e.g. b_{60}/p in the form:

$$\frac{b_{60}}{p} = \frac{60A}{p}\left(\frac{\gamma}{\sum t_v^2 c_0} - \frac{\sum t_v}{\sum t_v^2}\right)$$

This gives the following factor representing limits of confidence comparable with those of the standard error:

$$\frac{60A}{p}\left(\frac{\gamma - 1.4\, d(\gamma)}{\sum t_v^2 \{c_0 + 1.4\, d(c_0)\}} - \frac{\sum t_v}{\sum t_v^2}\right),$$

$$\frac{60A}{p}\left(\frac{\gamma + 1.4\, d(\gamma)}{\sum t_v^2 \{c_0 - 1.4\, d(c_0)\}} - \frac{\sum t_v}{\sum t_v^2}\right)$$

Table 34 shows some examples, where the limits of confidence have been calculated all the factors examined, corresponding to the standard error. They give a view of the effect on the accuracy of the factors of the methodical error.

From a comparison of the errors due to the method, as shown in Table 34, with the individual differences in these factors, it is evident

TABLE 34

EXAMPLES OF THE EFFECT OF THE METHODICAL ERROR ON THE ACCURACY OF THE CONSTANTS

No.	From t_f to t_l	β	r	b_{60}	$\frac{b_{60}}{p}$	T
114	40—350	0.0028±0.000035	−0.005 0.573 +0.005	−0.08 5.73 +0.07	−1.4 95.6 +1.1	−1.8 63.1 +0.7
10	60—350	0.0017±0.000040	−0.011 0.831 +0.012	−0.06 4.55 +0.06	−2.2 84.3 +1.9	−1.4 67.6 +1.4
20	90—350	0.0021±0.000046	−0.007 0.611 +0.008	−0.12 5.70 +0.12	−1.7 78.0 +1.7	−1.4 73.1 +1.4

that the latter observed differences due to individual characteristics are of a much greater order than those produced by the methodical error.

The statistical criteria of the above factors, the mean, the standard error of mean, and its standard deviation, which are collected in Table 37 and which have been mentioned in several contexts, have been calculated by the usual methods (Cramér 1949). They show, of course, the effect on the distribution of the above factors of both the individual variability and of the methodical inaccuracy.

ANALYSIS OF RESULTS

One of the primary aims of the investigation was to study how some diseases affect the metabolism of alcohol. The results show that particularly in NCA and hepatitis patients, the values of β and of b_{60}/p, which are those most interesting in this respect, are smaller than in healthy subjects. By using statistical methods, the degree of significance with which these results are to be regarded can be assessed.

Since the number of cases is comparatively small in each group, the most reliable results are obtained in this respect by using Student's t-test (Cramér 1949). It assumes that the factors examined in each group show a normal distribution. Such an assumption is made in the following, mostly on account of the observed distribution of β and b_{60}/p in the greatest groups (healthy men and women).

If the values of β of *e.g.* healthy men are denoted β_1, $\beta_2 \cdots \beta_{19}$ and the mean β, and the respective values of the NCA men β'_1, $\beta'_2 \cdots \beta'_{11}$ and β', and the following formula is calculated in order to test the difference $\beta - \beta'$

$$t = (\beta - \beta') \sqrt{\frac{19 \times 11 \times (19 + 11 - 2)}{(19 + 11)\left\{\sum_{i=1}^{19} (\beta_i - \beta)^2 + \sum_{i=1}^{11} (\beta'_i - \beta')^2\right\}}}$$

a corresponding percentage p is found in the t-table. The statisticians use the following expression: *if* $5\ \% > p > 1\ \%$, the difference is almost significant, if $1\ \% > p > 0.1\ \%$, the difference is significant, and if $0.1\ \% > p$, the difference is highly significant.

When the above is taken into account, Table 35 indicates the results of the testing. Because of the structure of the t-table, exact

TABLE 35

THE INFLUENCE OF SOME DISEASES ON THE VALUES OF β AND $\frac{b_{60}}{p}$, AS TESTED WITH STATISTICAL METHODS

Groups tested	$\beta - \beta'$		$\frac{b_{60}}{p} - \frac{b'_{60}}{p}$	
	p between	Order of significance	p between	Order of significance
Healthy male—healthy female	5.0 % — 2.0 %	almost significant	35 % — 30 %	
,, male—NCA male	0.1 % — 0 %	highly significant	0.1 % — 0 %	highly significant
,, female—NCA female	7.0 % — 5.0 %	not far from "almost significant"	1.0 % — 0.1 %	significant
,, male—hepatitis male	1.0 % — 0.1 %	significant	25 % — 20 %	
,, female—hepatitis female	0.1 % — 0 %	highly significant	2.0 % — 1.0 %	almost significant
,, male—diabetes male	30 % — 25 %			
,, female—diabetes female	8.0 % — 6.0 %	not far from "almost significant"		

values for p are not given, but the limits of p are indicated in each case.

The testing thus confirms the results in the hepatitis and NCA groups which are treated above, except for b_{60}/p in the male hepatitis group. The material comprises 8 cases in this group, and six of the patients were re-examined after, or during, recovery. In five of the cases the re-examination shows a remarkably high value of b_{60}/p, and it seems that chance has brought subjects with a high value of b_{60}/p while healthy to this group, and their b_{60}/p did not fall in hepatitis very much below the average of healthy subjects.

As the Table 35 indicates, it was also tested whether the observed difference between the values of β and b_{60}/p in the groups of healthy men and women were significant. For β, the result is confirmed, but for b_{60}/p, it is negative.

XI

EXAMINATION OF THE RESULTS

The normal concentration of alcohol in the blood of the healthy subjects, 0.012 $^0/_{00}$ as determined with the aid Widmark's micro-method, is slightly lower than mentioned in general in literature. Further, the endogenous alcohol of the male subjects was a little lower than that of the females. However, the concentrations were too low to give basis for any definite conclusions as to this difference, or as to the observed slight variation of the basal values in the course of the day, for the values vary within the range of the methodical error.

The average basal value of the blood of diabetic patients, 0.016 $^0/_{00}$, is a little above the mean of the healthy subjects. To what extent the possible presence of ketone bodies in the blood of diabetic patients raises the values obtained with Widmark's method and what proportion of the observed values is due to the true normal alcohol content of the blood, can not be judged with the aid of the method employed. No correlation was observed between blood sugar level and the concentration of the endogenous alcohol. On the other hand, those cases of diabetes which had negative results in the tests for urinary ketone bodies, showed the lowest basal values. In every case with positive results in Gerhard's and Legal's tests, the endogenous alcohol concentration in blood exceeded the mean of the diabetes group as a whole. The basal values obtained on a single subject during the same day vary very little from hour to hour. However, on different days their blood samples may show varying amounts of oxidizable volatile substances. The amount of easily oxidizable volatile substances has evidently been rather low in the abstaining, fasting diabetic subjects in the present material, for the maximum value obtained with Widmark's method was 0.061 $^0/_{00}$.

All subjects were given the alcohol on an empty stomach, in equal amounts and in the same concentration, and stress was laid on an ingestion of the alcohol in a short time equal in each case. Only this makes a comparison of the initial parts (resorption and diffusion phase) of the alcohol curves feasible in the material as whole.Nevertheless, the coincidence of an analysis — taken at a fixed time — with the true maximum of the curve is uncertain, and conclusions can be made only with reservation from the initial part of the curve. Since it is known that the absorption of alcohol from the stomach and the maximum concentration of blood alcohol both depend *e.g.* on the concentration of alcohol, on the pace at which it is ingested, and on the relation of the ingestion with intake of food, it is important to consider all the above factors when comparing the initial part of the blood alcohol curve as observed by different authors.

After an ingestion of alcohol (0.5 g per kg body weight, as a 40 per cent (by weight) aqueous solution) the blood alcohol curve rose rapidly in the group of the healthy subjects, and the maximum concentration was as a rule attained within 40 minutes (Fig. 11). The elimination of alcohol occurred at an even rate.

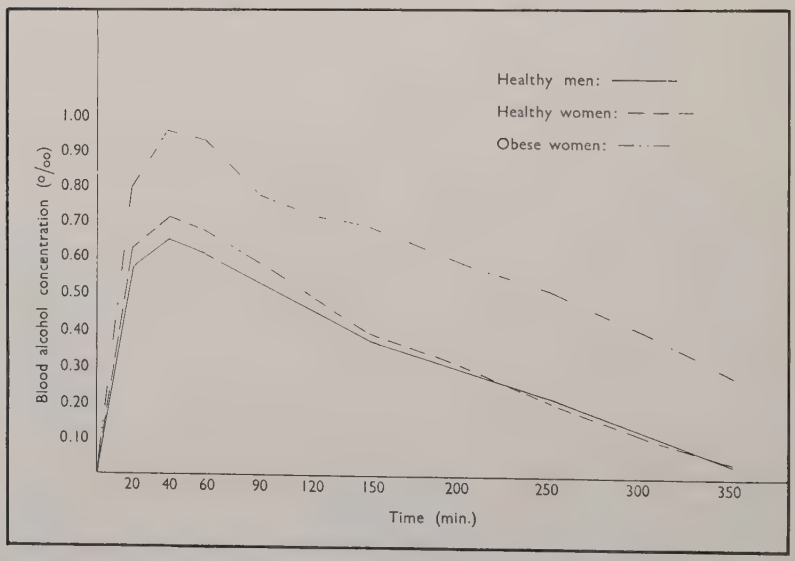

Fig. 11.— The average course of the blood alcohol curves of healthy men (19), healthy women (23), and of obese women (3).

TABLE 36

THE DISTRIBUTION OF THE CONSTANTS β AND r IN THE WHOLE MATERIAL, ARRANGED ACCORDING TO NUMERICAL VALUES

	Healthy			Obesity			Neurocirculatory asthenia			Acute hepatitis			Liver cirrhosis			Hyperthyreosis			Diabetes mellitus			The material as a whole
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	
β																						
<0.0012	—	—	—	—	—	—	—	—	—	1	—	1	—	—	—	—	—	—	1	—	1	2
0.0012—0.0014	—	—	—	—	—	—	4	1	5	3	1	4	—	—	—	—	1	1	3	2	5	15
0.0015—0.0017	5	1	6	—	1	1	4	1	5	2	5	7	2	1	3	—	3	3	3	3	6	31
0.0018—0.0020	7	6	13	—	1	1	2	1	3	1	3	4	2	—	2	—	1	1	3	—	3	27
0.0021—0.0023	4	9	13	—	1	1	1	3	4	1	2	3	—	—	—	—	3	3	2	1	3	27
0.0024—0.0026	2	5	7	—	—	—	—	—	—	—	—	—	—	—	—	3	1	4	—	1	1	12
0.0027—0.0029	1	2	3	—	—	—	—	—	—	—	—	—	—	—	—	—	2	2	—	1	1	6
0.0030—0.0032	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	1	—	—	—	1
>0.0032	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	1	1
r																						
<0.50	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
0.51—0.55	—	3	3	—	1	1	—	2	2	—	—	—	—	—	—	2	3	5	1	—	1	12
0.56—0.60	5	4	9	—	—	—	1	—	1	—	—	—	—	—	—	—	1	1	—	1	1	12
0.61—0.65	1	5	6	—	1	1	—	1	1	—	1	1	—	—	—	—	—	—	1	—	1	10
0.66—0.70	2	4	6	—	—	—	4	1	5	—	4	4	2	—	2	—	2	2	—	1	1	20
0.71—0.75	3	4	7	—	—	—	—	1	1	1	1	2	1	—	1	—	—	—	4	1	5	16
0.76—0.80	4	2	6	—	—	—	2	—	2	—	2	2	1	—	1	1	3	4	2	—	2	17
0.81—0.85	1	—	1	—	—	—	1	—	1	3	1	4	—	1	1	—	1	1	1	1	2	10
0.86—0.90	3	1	4	—	—	—	3	—	3	1	1	2	—	—	—	—	1	1	—	3	3	13
>0.90	—	—	—	—	—	—	—	1	1	3	1	4	—	—	—	—	1	1	4	1	5	11

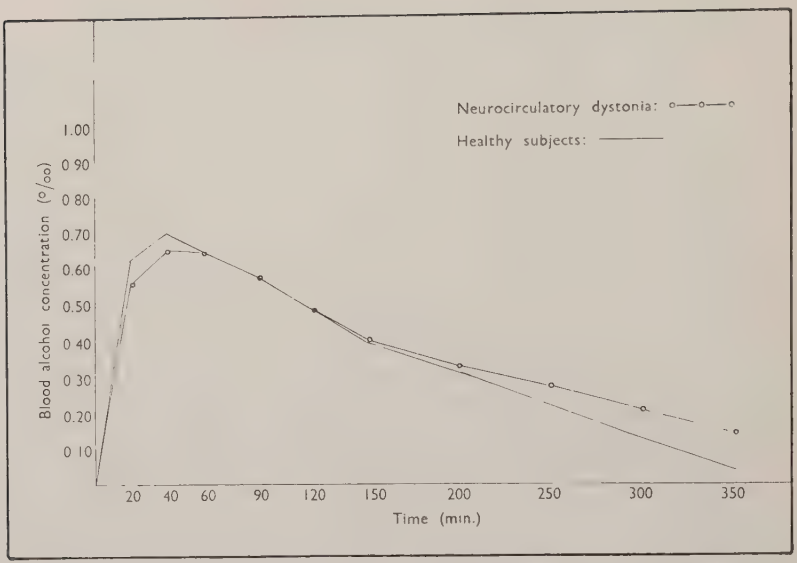

Fig. 12.— The average course of the blood alcohol curve of patients (17) suffering from neurocirculatory asthenia or dystonia.

The factor β is slightly lower in healthy men than in healthy women (*Table* 36 *and* 37). *However the difference is statistically only almost significant.*

The factor r *is* 0.72 ± 0.023, *with* $\sigma = \pm 0.102$ *in men and* 0.66 ± 0.018, *with* $\sigma = \pm 0.085$, *in women.* The latter constant evidently depends on the constitution. The highest values of r are met with in the athletic type and the second highest in asthenic subjects.

The ability to metabolize alcohol, b_{60}, is slightly higher in men than in women. On the other hand, *a woman seems to be able to eliminate alcohol as least as well as a man if calculated per kg body weight and hour.*

Persons suffering from *neurocirculatory asthenia or dystonia* as a rule have a record of low alcohol tolerance, and even a small amount of alcohol makes them tired and precipitates cardiac symptoms. After an ingestion of alcohol the initial part of their blood alcohol curve more or less resembles curves obtained on healthy subjects. However, in the postabsorptive phase their curves fall more slowly (Fig. 12). *The rate of elimination seems to be slower in NCA patients than in normal subjects.* Perhaps this is one reason for their generally poor alcohol tolerance in comparison with that of healthy subjects.

The value of r in the male subjects of this group is somewhat higher than normal, but most of the subjects have an athletic constitution. *Both* b_{60} and b_{60}/p *are smaller than the values observed in healthy subjects* (Table 37).

According to Kerppola (1950) the storage of glycogen is disturbed in NCA, and as a consequence, symptoms of hypoglycaemia occur, in particular during fasting. It is not impossible that the poor alcohol tolerance of NCA patients is connected with this phenomenon. A poor storage of glycogen may be followed by a disturbed glycolysis, and on the other hand, oxidation of alcohol may depend on the glycolysis.

The initial part of the blood alcohol curve of subjects suffering from *acute hepatitis* is comparable with that of normal cases, but the fall from the maximum may be a little steeper and faster than in healthy subjects. Further, the curve falls a little below normal. It seems as if the diffusion of alcohol from blood into tissues occurs for some reason somewhat more easily in hepatitis patients than in healthy subjects. In the postabsorptive phase, after a diffusion equilibrium is attained, the curve is slightly lower than in health and falls more slowly (Fig. 13). The value of β *is lower than in healthy*

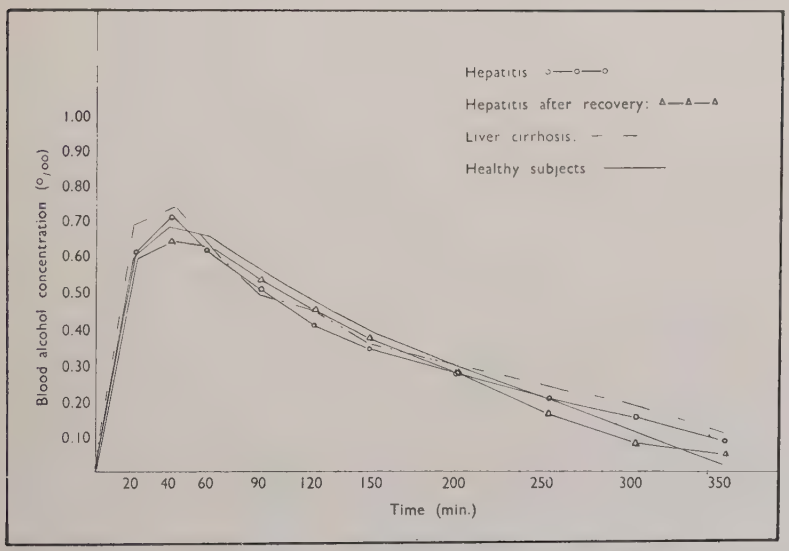

Fig. 13.— The average course of the blood alcohol curves of patients suffering from hepatitis (19), of hepatitis patients at a later control study (11), and of patients with liver cirrhosis (5).

TABLE 37

THE AVERAGE VALUES OF THE CONSTANTS IN THE WHOLE MATERIAL

	Sex	Number of cases	β	r	b_{60}	$\frac{b_{60}}{p}$	T
Healthy	M	19	0,00199±0,00007 σ = ±0,00032	0,722±0,023 σ = ±0,102	5.60±0,20 σ = ±0,86	83.8± 1.2 σ = ± 5.4	76.1± 2.8 σ = ±12.2
	F	23	0,00220±0,00007 σ = ±0,00033	0,657±0,018 σ = ±0,085	5.05±0.16 σ = ±0,78	85.7± 1.4 σ = ± 6.7	64.5± 2.4 σ = ±11.5
Obesity	M	—	—	—	—	—	—
	F	3	0,00197±0,00014 σ = ±0,00025	0,530±0,061 σ = ±0,105	7.19±0,32 σ = ±0,55	61.9± 6.1 σ = ±10.6	97.7± 6.3 σ = ±10.8
Neurocirculatory asthenia or dystonia (NCA)	M	11	0,00157±0,00008 σ = ±0,00026	0,764±0,031 σ = ±0,102	4.75±0,24 σ = ±0,80	70.1± 1.8 σ = ± 6.0	75.0± 2.8 σ = ± 9.3
	F	6	0,00190±0,00014 σ = ±0,00034	0,677±0,061 σ = ±0.148	4.45±0,24 σ = ±0,59	75.1± 2.9 σ = ± 7.3	62.2± 3.6 σ = ± 8.8
Acute hepatitis	M	8	0,00154±0,00013 σ = ±0,00037	0,865±0,027 σ = ±0,076	5.22±0,32 σ = ±0,91	78.6± 5.6 σ = ±15.8	83.6± 1.6 σ = ± 4.5
	F	11	0,00176±0,00008 σ = ±0,00026	0,757±0,031 σ = ±0,103	4.42±0,26 σ = ±0,86	78.2± 2.9 σ = ± 9.5	64.9± 4.0 σ = ±13.2

Liver cirrhosis	M	4	0,00175±0,00010 σ = ±0,00019	0,715±0,019 σ = ±0,039	5.33±0,53 σ = ±1.05	75.0± 2.8 σ = ± 5.7	76.9± 5.4 σ = ±10.8
	F	1	0,0016	0,83	2.62	79.5	40.6
Hyperthyreosis	M	3	0,00250±0,00006 σ = ±0,00010	0,610±0,081 σ = ±0,140	6.10±0,99 σ = ±1.41	90.7±10.7 σ = ±18.5	71.5±12.1 σ = ±21.0
	F	12	0,00218±0,00015 σ = ±0,00051	0,713±0,042 σ = ±0,140	4.77±0,29 σ = ±1.01	89.3± 3.2 σ = ±11.0	61.0± 2.8 σ = ± 7.9
Diabetes mellitus	M	13	0,00180±0,00017 σ = ±0,00060	0,806±0,047 σ = ±0,169	5.26±0,27 σ = ±0,98	82.6± 2.6 σ = ± 9.4	76.7± 2.8 σ = ±10.2
	F	8	0,00188±0,00019 σ = ±0,00053	0,801±0,047 σ = ±0,126	5.14±0,26 σ = ±0,75	86.1± 3.6 σ = ±10.3	73.4± 2.4 σ = ± 6.9

subjects, and the value of r is *higher*. *The ability to metabolize alcohol is also lower in the women of this group than in healthy subjects*, respectively (Table 37). In re-examined cases, after the disappearance of jaundice or while it was about to disappear, the rate of elimination and the ability to metabolize alcohol improve both. At the same time the value of r is reduced (Table 22).

The blood alcohol curve of the *liver cirrhosis* cases resembles that of the hepatitis patients. (Fig. 13). The values of the constants β and r and the ability to metabolize alcohol are shown in Table 37. Because of the small number of cases in this group, the results are not compared statistically with those of healthy subjects, and therefore, no definite conclusions can be made.

The blood alcohol curve of the *hyperthyreotic* patients remains slightly lower than that of the healthy subjects. When four female hyperthyreotic patients were re-examined after treatment, the blood alcohol curve was slightly higher than during the illness (Fig. 14). *The rate of elimination and the value of r were in the greater, female, group approximately the same as in healthy subjects*, and the number of the men was too small to justify any conclucions (Table 37).

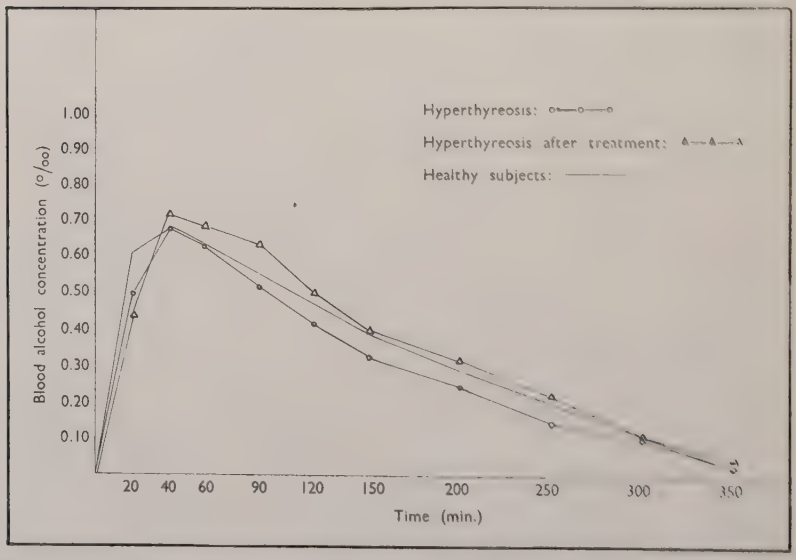

Fig. 14.—The average course of the blood alcohol curves of hyperthyreotic patients (15) and of hyperthyreotic patients after treatment (4).

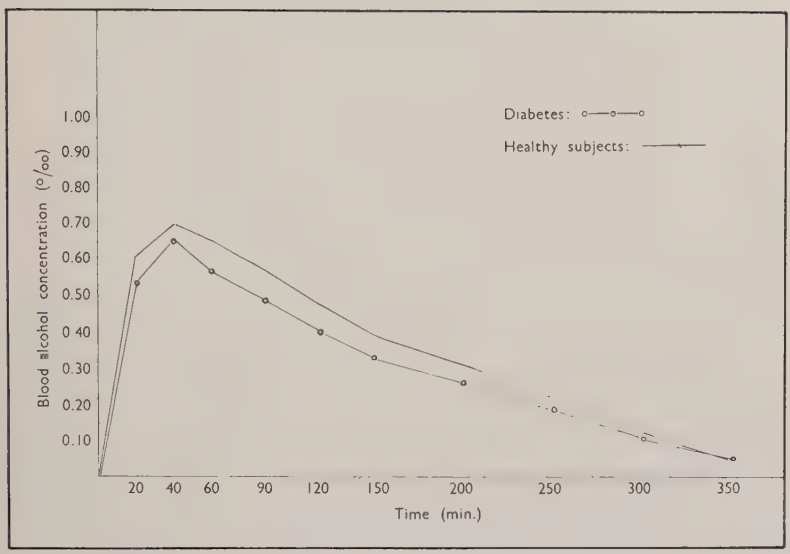

Fig. 15.— The average course of the blood alcohol curve of diabetic patients (21).

A remarkable finding are the several rather low curves met with in the *diabetes* group (Fig. 15). In many cases, the maximum seems to remain particularly low. It is difficult to judge whether this is due to an incomplete absorption of alcohol from the stomach or to an acceleration of its diffusion in connection with the absorption. It seems improbable that alcohol would have been lost in the analyses of just this, diabetes, group. On the other hand, there are in this group several cases with a rapidly attained and high maximum. After an attained maximum, the curve falls steeply in these cases. The mean blood alcohol curve of the diabetic patients remains slightly below that of normal subjects, and falls in the terminal part perhaps a little more slowly. However, the *rate of disappearance of alcohol and the ability to metabolize it must be regarded as identical with those of healthy subjects*, as indicated in the statistical treatment of the results.

XII

SUMMARY

An account is given of experimental blood alcohol studies made at the First Medical Clinic of the University, Helsinki, during the years 1948—1950. The determinations of the endogenous blood alcohol were made on 165 blood samples taken from 74 subjects. Blood alcohol determinations after ingestion of alcohol were performed on 1420 samples of blood taken from 124 subjects. The alcohol analyses were made by using Widmark's micromethod, on the blood of subjects given 0.5 g of absolute alcohol per kg body weight, as a 40 per cent (by weight) aqueous solution which the subjects ingested by mouth within a short time. The samples for the blood alcohol concentration were taken at 20, 40, 60, 90, 120, 150, 200, 250, 300, and 350 minutes after the ingestion of alcohol.

1. The group of *healthy subjects* comprised 19 men and 23 women. The constant β was in *men* 0.0020 (0.00199) $\pm$ 0.00007, *with a standard deviation of* 0.00032, and in *women* 0.0022 (0.00220) $\pm$ 0.00007, *with a standard deviation of* $\pm$ 0.00033. The *difference* between the values of β *for men and women is statistically almost significant.* The *ability to metabolize alcohol per hour and kg body weight* (b_{60}/p) was in *men* 83.8 *mg* $\pm$ 1.2, *with a standard deviation of* $\pm$ 5.4, and *in women* 85.7 *mg* $\pm$ 1.4, *with a standard deviation of* $\pm$ 6.7. The *difference* between the values of b_{60}/p *of men and women is not significant.* The factor r was in *men* 0.72 (0.722) $\pm$ 0.023, *with a standard deviation of* $\pm$ 0.102, *and in women* 0.66 (0.657) $\pm$ 0.018, *with a standard deviation of* 0.085.

2. The group of *patients* comprised 17 subjects affected with *neurocirculatory asthenia or dystonia* (*NCA*), 19 cases of *acute hepatitis*, 5 cases of *liver cirrhosis*, 15 cases of *hyperthyreosis*, and 21 cases of *diabetes mellitus.*

a) *The* β *of the male NCA patients was* 0.0016 (0.00157) $\pm$ 0.00008, *with a standard deviation of* $\pm$ 0.00026, and that of the *females* 0.0019 (0.00190) $\pm$ 0.00014, *with a standard deviation of* $\pm$ 0.00034. The value of β was *in NCA men* smaller than in the group of *healthy men*, and *statistically the difference is highly significant.* The difference between the values of β *for healthy and NCA women is* not far from "*almost significant*". The factor b_{60}/p *was* 70.1 *mg* $\pm$ 1.8, *with a standard deviation of* $\pm$ 6.0 *for the men*, and 75.1 *mg* $\pm$ 2.9, *with a standard deviation of* $\pm$ 7.3, *for the women of this group.* As *compared* with the group of *healthy subjects*, the difference of *NCA men is highly significant*, and that of *women significant. The factor r of the men was* 0.76 (0.764) $\pm$ 0.031, *with a standard deviation of* $\pm$ 0.102, *and that of women* 0.68 (0.677) $\pm$ 0.061, *with a standard deviation of* $\pm$ 0.148.

b) *The* β *of the male patients of the acute hepatitis group was* 0.0015 (0.00154) $\pm$ 0.00013, *with a standard deviation of* $\pm$ 0.00037, *and that of the females* 0.0018 (0.00176) $\pm$ 0.00008, *with a standard deviation of* $\pm$ 0.00026. The β of the *male hepatitis* patients was lower than that of *healthy men* and the difference is statistically *significant. The difference* between the β of *healthy women* and of the *female hepatitis* patients *is highly significant.* b_{60}/p *was* 78.6 *mg* $\pm$ 5.6, *with a standard deviation of* $\pm$ 15.8, *in the group of male hepatitis patients, and* 78.2 *mg* $\pm$ 2.9, *with a standard deviation* $\pm$ 9.5 *in the corresponding female group.* The *difference* in a comparison *with healthy subjects* is *not significant* for the *men* whereas it is *almost significant* for the *women.* The factor *r* was 0.87 (0.865) $\pm$ 0.0027, *with a standard deviation* $\pm$ 0.076 *for the men, and* 0.76 (0.757) $\pm$ 0.031, *with a standard deviation of* $\pm$ 0.103, *for the women.*

c) In cases of *liver cirrhosis*, it seems that the factors β and b_{60}/p remain *slightly lower than the factors in healthy subjects*, respectively.

d) The results of the *hyperthyreosis* and *diabetes mellitus* groups appear to be rather *similar as in healthy subjects.*

3. The mean value of the concentration of alcohol and of other volatile, easily oxidizable substances eventually present in the blood of fasting, abstaining diabetic subjects was 0.016 $^0/_{00}$, whereas the corresponding figure for healthy subjects was 0.012 $^0/_{00}$.

XIII

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